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Identification and Listing of Hazardous Waste Under RCRA (Resource Conservation and Recovery Act), Subtitle C, Section 3001; Health and Environmental Effect Profiles (40 CFR 261)

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This appendix describes health and environmental effect profiles compiled to support the listing of approximately 170 of the hazardous constituents identified on Appendix VIII in the regulations (40 CFR, Part 261). These profiles are also being used to support the listing of hazardous wastes in Subpart D of Part 261, due to the presence in the wastes, of these hazardous constituents. Many of these profiles have been summarized from the water quality criteria documents prepared in support of various programs under the Clean Water Act.

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IDENTIFICATION AND LISTING OF HAZARDOUS WASTE UNDER RCRA, SUBTITLE C, SECTION 3001

Health and Environmental Effect Profiles
(40 CFR 261)

This document (ms. 1941.29) provides background information and support for EPA's hazardous waste regulations

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October 1980

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CASE FILE

ATTENTION

AS NOTED IN THE NTIS ANNOUNCEMENT, PORTIONS OF THIS REPORT ARE NOT LEGIBLE. HOWEVER, IT IS THE BEST REPRODUCTION AVAILABLE FROM THE COPY SENT TO NTIS.

Preface

These health and environmental effect profiles have been compiled to support the listing of approxmately 170 of the hazardous constituents identified on Appendix VIII in the regulations (40 CFR, Part 261). These profiles are also being used to support the listing of hazardous wastes in Subpart D of Part 261, due to the presence in the wastes, of these hazardous constituents. Many of these profiles have been summarized from the water quality criteria documents prepared in support of various programs under the Clean Water Act. In each case, however, the document is based on information and references available to the Agency and which are referenced in each individual document.

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No. 1

Acetaldehyde

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

ACETALDEHYDE

Summary

An increased incidence of malignant neoplasms was reported in workers in an aldehyde factory. Acetaldehyde was found in concentration of 1 to 7 mg/m^3 but there was no indication that acetaldehyde was the causative factor for the cancers.

Equivacol results were obtained from a number of mutugenicity assays.

I. INTRODUCTION

Acetaldehyde (CH_3COH) is a clear, flammable liquid with a pungent, fuity odor. It has the following physical/chemical properties (Hawley, 1977; U.S. EPA, 1976a):

Chemical Structure:	$CH_3 - C(=O)H$
CAS No.:	75-07-0
Molecular Formula:	C_2H_4O
Boiling Point:	20.2°C
Melting Point:	-123.5°C
Vapor Pressure:	740 mm (20°C)
Density:	0.7834 at 18°C/4°C
Octanol/Water Partition Coefficient:	0.43
Vapor Density:	1.52
Solubility:	soluble in water and most organic solvents

A review of the production range (includes importation) statistics for acetaldehyde (CAS No. 75-07-0) which was listed in the initial TSCA Inventory (1977) has shown that between 1 billion and 2 billion pounds of this chemical were produced/imported in 1977.*/

Acetaldehyde is used mainly as a chemical intermediate in the production of paraldehydes, acetic acid, acetic anhydride, and a variety of other chemicals (Hawley, 1977).

II. EXPOSURE

The NIOSH National Occupational Hazard Survey estimates that 2,430 workers are exposed to acetaldehyde annually (1976).

A. Environmental Fate

The available data do not indicate a potential for persistance and accumulation in the environment. While there is little information on the environmental fate of acetaldehyde, the BOD/COD of 0.72 confirms that acetaldehyde will readily biodegrade (Verschueren, 1978).

As to its fate in air, aldehydes are expected to photodissociate rapidly and competively with their oxidation for a half-life of 2 to 3 hours. Aldehydes do not persist in the atmosphere but the fact that acetaldehyde is a component of vehicle exhaust may be significant in its contribution to smog (U.S. EPA, 1977b).

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*/ This production range information does not include any production/importation data claimed as confidential by the person(s) reporting for the TSCA Inventory, nor does it include any information which would compromise Confidential Business Information. The data submitted for the TSCA Inventory, including production range information, are subject to the limitations contained in the Inventory Reporting Regulation (40 CFR 710).

B. Bioconcentration

Acetaldehyde has an octanol/water partition coefficient of 0.43 indicating that it is highly hydrophilic and should not accumulate (U.S. EPA, 1976).

C. Environmental Occurrence

Acetaldehyde is a normal intermediate product in the respiration of higher plants; it occurs in traces in ripe fruits and may form in alcoholic beverages after exposure to air. It has been reported that acetaldehyde is found in leaf tobacco, cigarette smoke, and automobile and diesel exhaust (U.S. EPA, 1977a). Acetaldehyde has been reported in both finished drinking water supplies and effluents from sewage treatment plants in several locations throughout the U.S. (EPA, 1976b).

III. PHARMACOKINETICS

Acetaldehyde which is the first occurring metabolite of ethanol in mammals is produced in the liver and is often found in various tissues after the consumption of alcohol (Obe and Ristow, 1977). It is an intermediate product in the metabolism of sugars in the body and hence occurs in traces in blood (EPA, 1977b).

IV. HEALTH EFFECTS

A. Carcinogenicity

Watanabe and Sugimoto (1956) administered 0.5-5% acetaldehyde subcutaneously to rats for a period of 489 to 554 days. Four of the 14 animals developed spindle cell carcinomas at the site of injection.

An increased incidence of malignant neoplasms has been observed in workers at an aldehyde factory who were exposed to acetaldehyde,

butyraldehyde, crotonaldehyde, aldol, several alcohols, and longer chain aldehydes. Acetaldehyde was found in concentrations of 1-7 mg/m^3. Of the 220 people employed in this factory, 150 has been exposed for more than 20 years. During the period 1967 to 1972, tumors were observed in nine males (all of whom were smokers). The tumor incidences observed in the workers exceeded incidences of carcinomas of the oral cavity and bronchogenic lung cancer expected in the general population and, for the age group 55-59 years, the incidence of all cancers in chemical plant workers. There is no indication that acetaldehyde was the causative factor in the excess incidence of cancer (Bittersohl, 1974; Bittersohl, 1975).

Acetaldehyde has been found positive in a variety of mutagenicity tests: siter chromatid exchange in cultured human lymphocytes and a Chinese hamster (ovary) cell line (Ristow and Obe, 1978; Obe and Ristow, 1977); S. typhimirium (Ames Test); (Pol A$^-$) E. coli (Rosenkranz, 1977); and WP2 uvrA trp$^-$) E. coli (Veghelyi et al., 1978). It has, however, also been reported negative by other investigators: S. typhimurium, with and without activation (Cotruvo et al., 1977; Commoner, 1976; Laumbach et al., 1977); Saccharomyces cerevisiae test for recombination (Cotruvo et al., 1977); and Bacillus subtilis repair essay (Laumbach et al., 1977). Thus, of ten reports of in vitro tests for the mutagenicity of acetaldehyde, 5 were positive and 5 were negative. Acetaldehyde was also found to cross-link isolated calf thymus DNA (Ristow and Obe, 1978).

C. Other Toxicity

1. Acute

A table summarizing the acute toxicity of acetaldehyde in rats and mice is found below:

Species	Dose	Route	Result	Reference
rat	16,000ppm x 4 hrs.	ihl	lethal	Smyth, 1956
rat	4,000ppm x 4 hrs.	ihl	lethal	NIOSH, 1977
rat	640 mg/kg	s.c.	LD_{50}	Skog, 1950
rat	20,000ppm x 30 min.	ihl	LC_{50}	Skog, 1950
rat	1,930 mg/kg	oral	LD_{50}	NIOSH, 1977
mouse	560 mg/kg	s.c.	LD_{50}	Skog, 1950
mouse	1,232 mg/kg	oral	LD_{50}	NIOSH, 1977

D. Other Relevant Data

Acetaldehyde is a mucous membrane irritant in humans (Verschueren, 1978).

V. AQUATIC EFFECTS

A. Acute

The 24-hour median threshold limit (TLm) for acetaldehyde pinperch is 70 mg/l. The 96-hour TLm in sunfish is 53 mg/l (Verschueren, 1978).

VI. EXISTING GUIDELINES

A. Humans

The American Conference of Governmental and Industrial Hygienists (ACGIH) has adopted a Threshold Limit Value (TLV) of 100 ppm for acetaldehyde. The OSHA standard in air is a Time Weighted Average (TWA) of 200 ppm.

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No. 2

Acetonitrile

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

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ACETONITRILE

SUMMARY

Depending on the amount absorbed, acetonitrile may cause disorders in the central nervous system, liver, kidneys, cardiovascular system and gastrointestinal system, regardless of the route of administration. These effects are attributed to the metabolic release of cyanide from the acetonitrile molecule, although the parent molecule itself may cause these effects.

This Hazard Assessment Profile was based largely on information obtained from NIOSH and its Criteria for a Recommended Standard: Occupational Exposure to Nitriles, (NIOSH, 1978).

The NIOSH 1972-1974 National Occupational Hazards Survey estimates that about 26,000 workers are occupationally exposed to nitriles.

Major occupational exposures to nitrile occur by inhalation of vapor or aerosols and by skin absorption. Adverse effects of nitriles are also found from eye contact.

There is no available evidence to indicate that acetonitrile has mutagenic or carcinogenic activity. Two studies have reported teratogenic effects in rats.

Unlike the immediate onset of cyanide toxicity, nitrile poisoning displays a delayed onset of symptoms.

I. INTRODUCTION

Acetonitrile (CH_3CN) is a mononitrile and falls into the saturated aliphatic class of nitriles. It is a colorless liquid and has a vapor pressure of 73 mm Hg at 20° C. It has a molecular weight of 41.05 and a specific gravity of 0.786 (NIOSH, 1978).

When heated to decomposition, nitriles emit toxic fumes containing cyanides (Sax, 1968).

Acetonitrile was introduced to the commerical market in 1952, and its industrial uses lie in the manufacture of plastics, synthetic fibres, elastomers, and solvents. Acetonitrile is used as a solvent in the extractive distillation that separates olefins from diolefins, butadiene from butylene, and isoprene from isopentane.

In 1964, 3.5 million pounds of acetonitrile were consumed industrially.

II. EXPOSURE

A. Water and Food

Pertinent data were not found in the available literature.

B. Inhalation

Acetonitrile can be readily absorbed from oral mucosa (McKee, et al. 1962; Dalhamn, et al. 1968).

In the workplace, acute poisoning and death have been reported following the inhalation of acetonitrile (Dequidt, et al. 1974).

Studies have demonstrated that acetonitrile is absorbed by lung tissue (Dequidt, et al. 1974; Grabois, 1955; Amdur, 1959).

C. Dermal

Dermal exposures to acetonitrile have caused adverse reactions including death in some cases (NIOSH, 1978).

Acetonitrile has been reported to have been absorbed through the intact skin of rabbits, yielding a dermal LD_{50} of 980 mg/kg (Pozzani, et al. 1959).

III. PHARMACOKINETICS

A. Absorption

Acetonitrile is a component of cigarette smoke and is absorbed by the oral tissues (McKee, et al. 1962; Dalhamn, et al. 1968).

Humans have been shown to absorb acetonitrile directly through the skin and respiratory tract (Zeller, et al. 1969; Amdur, 1959; Dequidt, et al. 1974).

B. Distribution

Studies by McKee, et al. (1962) and Dalhamn, et al. (1968) show that acetonitrile from cigarette smoking is retained by the lungs.

Tissue distribution studies indicated that mononitriles (and acetonitrile, in particular) are distributed uniformly in the internal organs of humans and that cyanide metabolites are found predominantly in the spleen, stomach and skin, and to a lesser extent, in the liver, lungs, kidneys, hearts, brain, muscle, intestines, and testes (Dequidt, et al. 1974).

Haguenoer, et al. (1975) exposed three rats to 2,800 or 25,000 ppm acetonitrile by inhalation. At 25,000 ppm, all three rats died after 30 minutes. Chemical analysis

of the organs showed that the mean concentration of acetonitrile in muscle was 136 µg/100 g of tissue and 2,438 µg/100 g of kidney tissue. High acetonitrile excretion or possible renal blockage were postulated as the causes for the high renal concentration.

Nitriles and their metabolic products have been detected in urine, blood and tissues (McKee, et al. 1962).

C. Metabolism

Since human and animal studies report symptoms characteristics of cyanide poisoning, it is reasonable to assume that a portion of the effects of exposure to acetonitrile is due to the release of the cyanide ion from the parent compound (Zeller, et al. 1969; Amdur, 1959; Pozzani, 1959).

After absorption, nitriles may be metabolized to an alpha cyanohydrin or to inorganic cyanide, which is oxidized to thiocyanate and is excreted in the urine. The C=N group may be converted into a carboxylic acid derivative and ammonia, or may be incorporated into cyanocobalamine. Ionic cyanide also reacts with carboxyl groups and with disulfides (McKee, et al. 1962).

Haguenoer, et al (1975) injected white male Wistar rats with varying levels of acetonitrile ranging from 600 mg/kg to 2,340 mg/kg. At autopsy, the internal organs showed that the combined hydrogen cyanide consisted essentially of thiocyanates, cyanohydrins and cyanocobalamines.

D. Excretion

Acetonitrile is found in the morning urine of cigarette smokers. Concentrations of acetonitrile range from 2.2

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D. Excretion

Acetonitrile is found in the morning urine of cigarette smokers. Concentrations of acetonitrile range from 2.2

µg/100 ml urine for those smoking three cigarettes per day up to 20 µg/100 ml urine for heavy smokers (up to 2.5 packs per day). The results showed that acetonitrile, once absorbed into the body, can be excreted unchanged in the urine (McKee, et al. 1962).

Acetonitrile is also excreted unchanged in exhaled air (Haguenoer, et al. 1975).

IV. EFFECTS

A. Carcinogenicity

Dorigan, et al. (1976) failed to show significant carcinogenic effects in a two-year exposure study conducted with rats.

B. Mutagenicity

Pertinent data were not found in the available literature.

C. Teratogenicity

Intraperitoneal (i.p.) administration of acetonitrile to pregnant rats produced fetal malformations (Dorigan, et al. 1976). Schmidt, et al. (1976) have determined skeletal abnormalities in rats following i.p. exposure to acetonitrile.

D. Other Reproductive Effects

Pertinent data were not found in the available literature.

E. Chronic Toxicity

In an experiment to stimulate chronic occupational exposure (seven hours per day, five days per week), 30 rats were exposed to a concentration of 655 ppm acetonitrile for

90 days. The rats exhibited bronchial inflammation, desquamatization and hypersecretion of mucus, and hepatic and renal lesions. Monkeys exposed by the same regimen, but to 350 ppm acetonitrile for 91 days, experienced bronchitis and moderate hemorrhage of the superior and inferior sagittal sinuses of the brain (Pozzani, et al. 1959).

Dogs exposed to acetonitrile at a concentration of 300 ppm for 91 days showed a reduction in body weight as well as a reduction in hemoglobin and hematocrit values (Pozzani,, et al. 1959).

Monkeys exposed to 660 ppm acetonitrile per day showed poor coordination during the second week of exposure and a monkey exposed to 330 ppm showed hyperexcitability toward the end of the 13th week (Pozzani, et al. 1959).

The same investigators reported chronic LD_{50} values of 0.85 and 0.95 ml/kg for female rats which i.p. administration of acetonitrile.

G. Other Relevant Information

Dogs exposed with lethal quantities of acetonitrile (16,000 ppm for four hours) showed blood cyanide levels ranging from 305-433 µg/100 ml of blood after three hours (Pozzani, et al. 1959).

V. AQUATIC TOXICITY

A. Acute

Observed 96-hour LC_{50} values for the fathead minnow (Pimephales promelas) are 1020 mg/l in hardwater and 1000 ml/l in softwater (Bringmann, 1976). For bluegills, (Lepomis macrochirus) and guppies (Lebistes reticulatus), the

respective 96-hour values in softwater are 1850 mg/l and 1650 mg/l (Jones, 1971; Henderson, et al. 1960).

B. Chronic, Plant Effects, and Residue

Pertinent data were not found in the available literature.

C. Other Relevant Information

Acetonitrile has been observed to damage the bronchial epithelium of fish (Belousov, 1969). This compound, when added to the aqueous environment of roaches and filberts, disrupted blood circulation and protein metabolism and induced hyperemia, hemorrhages, and the appearance of small granules in the heart, brain, liver, and gills of fish. The hepatic glycogen level decreased sharply. CH_3CN induced-death apparently resulted from circulatory disturbances and necrobiotic changes in the cerebral neurons (Belousov, 1972).

Acetonitrile at a concentration of 100 mg/l inhibited nitrification in saprophytic organisms (Chekhovskaya, 1966).

VI. EXISTING GUIDELINES

A. Human

A federal occupational standard exists for acetonitrile and is based on the TLV for workplace exposure previously adopted by American Conference of Governmental and Industrial Hygienists. This TLV is 40 ppm (70 mg/m^3) and is an eight-hour TWA.

B. Aquatic

Pertinent data were not found in the available literature.

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No. 3

Acetophenone

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

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ACETOPHENONE

Summary

Acetophenone is present in various fossil fuel processes and products, particularly coal and petroleum products. It is used as a flavoring agent in products for human consumption and as an intermediate in organic synthetic processes, particularly plastics manufacturing.

No data on the potential for carcinogenic, mutagenic, or teratogenic effects or on the chronic toxicity of acetophenone were found in the available literature.

There are no existing OSHA, NIOSH, or ACGIH standards or guidelines. Acetophenone is a skin irritant and has been shown to cause severe eye irritation in rabbits at microgram quantities. Acetophenone is highly toxic to aquatic life

I. INTRODUCTION

Acetophenone (1-phenylethanone, phenyl methyl ketone, acetylbenzene, benzoyl methide, hypnone, $C_6H_5COCH_3$; molecular weight 120.15) is a liquid with a melting point of 20.5°C and is slightly soluble in water. Acetophenone is used to impart a pleasant jasmine or orange-blossom-like odor to perfumes, as a catalyst for the polymerization of olefins, and in organic syntheses, especially as a photosynthesizer (Windholz, 1976). Additionally, it is used as a tobacco flavoring, as a solvent or intermediate in the synthesis of pharmaceuticals, and as a by-product of the coal processing industry. Acetophenone is present in gasoline exhaust at less than 0.1 to 0.4 ppm (Verschueren, 1977).

II. EXPOSURE

No data on levels of acetophenone in food or water or on other potential (inhalation or dermal) exposures were found in the readily available literature.

III. PHARMACOKINETICS

Information on the absorption, distribution, metabolism, or excretion of acetophenone was not found in the readily available literature, despite the fact that it is used in pharmaceutical preparations and in tobacco, perfume, and other products for human comsumption.

IV. EFFECTS

A. Carcinogenicity, Mutagenicity, Teratogenicity, and Chronic Toxicity

Readily available data are extremely limited. One paper suggests the possible mutagenicity of acetophenone due to its ability to cause DNA breakage in bacterial systems following DNA photosensitization (Rahn, et al. 1974). Because of the particular sensitivity of the bacterial system to DNA breakage, this information by itself is insufficient to establish acetophenone as a mutagenic agent.

There is no additional data readily available on the potential for carcinogenic, mutagenic, or teratogenic activity by acetophenone. No data are available on chronic toxicity.

B. Acute Toxicity

Skin irritaion was observed in the rabbit at 10 mg/24 hrs. using the draize procedure and at 515 mg when applied to the skin in the absence of the absorbent gauze patch. Severe eye irritation was obtained in the rabbit following application of 771 ug of acetophenene. The oral LD_{50} in rats was 900 mg acetophenone/kg, while the lethal dose following intraperitoneal injection in mice was 200 mg/kg (NIOSH, 1978). Acetophenone is a hypnotic in high concentrations and was used as an anesthetic in the last century before less toxic substances were found (Kirk and Othmer, 1963).

C. Other Relevant Information

Based upon the retention time in a gas chromatographic/mass spectrographic column, Veith and Austin (1976) suggest a potential for bioaccumulation of acetophenone. There is no additional information available to verify this situation, however.

Microbial metabolism of acetophenone as the sole source of carbon and energy has been demonstrated in pure culture (Cripps, 1975).

V. AQUATIC TOXICITY

Based upon reported values in the literature, acetophenone has been shown to be highly toxic to aquatic life, (U.S. EPA, 1979). LC_{50} values for fathead minnow are reported for the following time periods: 1 hour, greater than 200 mg/l; 24 hours, 200 mg/l; 48 hours, 163 mg/l; 72 hours, 158 mg/l; and 96 hours, 155 mg/l (U.S. EPA, 1976).

Acetophenone has been reported to be a major constituent (36 percent) of a weathered bunker fuel. This suggests that it may be present in large quantity following spills of some bunker fuels (Guard, et al. 1975).

Bunker fuels are highly variable form refinery to refinery; thus, a blanket statement as to percentage composition of acetophenone or other constituents cannot be made.

VI. EXISTING GUIDELINES AND STANDARDS

There are no existing guidelines and standards from OSHA, NIOSH, or ACGIH. Similarily, no ambient water quality standards for acetophenone exist.

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No. 4

Acetyl Chloride

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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ACETYL CHLORIDE

Summary

Acetyl chloride is an irritant and a corrosive. Cutaneous exposure results in skin burns, while vapor exposure causes extreme irritation of the eyes and mucous membranes. Inhalation of two ppm acetyl chloride has been found irritating to humans. Death or permanent injury may result after short exposures to small quantities of acetyl chloride. An aquatic toxicity rating has been estimated to range from 10 to 100 ppm.

However, acetyl chloride reacts violently with water. Thus, its half-life in ambient water should be short and exposure from water should be nil. The degradation products should likewise pose no exposure problems if the pH of the water remains stable.

ACETYL CHLORIDE

I. INTRODUCTION

Acetyl chloride (ethanoyl chloride; CH_3COCl; molecular weight, 78.50) is a colorless, fuming liquid with a pungent odor, a boiling point of 51-52°C, and a melting point of -112°C (Windholz, 1976). It is used as an acetylating agent in testing for cholesterol and in the qualitative determination of water in organic liquids. It is miscible with benzene, chloroform, ether or glacial acetic acid (Windholz, 1976). In the presence of water or alcohol, however, acetyl chloride hydrolyzes violently to form hydrogen chloride and acetic acid. Phosgene fumes, which are highly toxic, are emitted when acetyl chloride is heated to decomposition (Sax, 1975).

The 1975 U.S. annual production of acetyl chloride was approximately 4.54×10^5 grams (SRI, 1976). During transportation, this chemical should be stored in a cool, well-ventilated place, out of direct sunlight, and away from areas of high fire hazard; it should periodically be inspected (Sax, 1975). Acetyl chloride must be protected from water (Windholz, 1976).

II. EXPOSURE

Acetyl chloride reacts violently with water (see above). Thus, its half-life in ambient water should be short and exposure from water should be nil. The degradation products should likewise pose no exposure problems if the pH of the water remains stable. Internal exposure to acetyl chloride will most likely occur through inhalation of the vapor, or, on rare occasions, through ingestion. Skin absorption is very unlikely although severe burns would be expected.

III. PHARMACOKINETICS

Pertinent data could not be located in the available literature.

IV. EFFECTS

Acetyl chloride is an irritant and a corrosive. Cutaneous exposure results in skin burns. Vapor exposure causes extreme irritation of the eyes and mucous membranes (Windholz, 1976). Inhalation of 2 ppm acetyl chloride was found irritating to humans (Handbook of Organic Industrial Solvents, 1961). Death or permanent injury may result after very short exposures to small quantities of acetyl chloride (Sax, 1975).

Because the toxicity of acetyl chloride might be expected to pattern that of its breakdown product hydrogen chloride (HCL), LC_{Lo} value (the lowest concentration of a substance in air which has been reported to cause death in humans or animals) for HCl might be indicative of its toxicity. This value in humans is 1000 ppm for one minute (Mason, 1974).

Pertinent information could not be located in the available literature regarding the carcinogenicity, mutagenicity, teratogenicity and chronic toxicity of acetyl chloride.

V. AQUATIC TOXICITY

Acetyl chloride has been shown to be toxic to aquatic organisms in the ranges of 10 to 100 ppm (Hann and Jensen, 1974). No other information has been found in the literature.

VI. EXISTING GUIDELINES AND STANDARDS

No standards for acetyl chloride have been reported. However, a ceiling limit of 5 ppm has been reported for hydrogen chloride (the most irratating hydrolysis product of acetyl chloride) in industrial exposures. (Mason, 1974).

ACETYL CHLORIDE

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No. 5

Acrolein

Health and Environmental Effects

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APRIL 30, 1980

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ACROLEIN

SUMMARY

Acrolein has not been shown to be a carcinogen or cocarcinogen in inhalation experiments. Acrolein is mutagenic in some assay systems. Information on teratogenicity is not available. The only reported chronic effect of acrolein in humans is irritation of the mucous membranes. Chronic exposure of Syrian golden hamsters to acrolein in the air caused reduced body weight gains and inflammation and epithelial metaplasia in the nasal cavity. In addition, females had decreased liver weight, increased lung weight, and slight hematologic changes.

Acrolein has been demonstrated to be acutely toxic in freshwater organisms at concentrations of 57 to 160 µg/l. A single marine fish tested was somewhat more resistant with a 48-hour LC_{50} of 240 µg/l. Toxicity to marine invertebrates was comparable to that of freshwater organisms.

ACROLEIN

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Acrolein (U.S. EPA, 1979).

Acrolein (2-propenal; CH_2=CHCHO; molecular weight 56.07) is a flammable liquid with a pungent odor. It has the following physical and chemical properties (Weast, 1975; Standen, 1967):

Melting Point	-86.95°C
Boiling Point Range	52.5 - 53.5°C
Vapor Pressure	215mm Hg at 20°C
Solubility	Water: 210.8 percent by weight at 20°C
Density	0.8410 at 20°C
Production (Worldwide)	59 kilotons (Hess, et al. 1978)
Capacity (Worldwide)	102 kilotons/year
Capacity (United States)	47.6 kilotons/year

Acrolein is used as a biocide, crosslinking agent, and tissue fixative. It is used as an intermediate throughout the chemical industry.

The fate of acrolein in water was observed in natural channel waters (Bowmer and Higgins, 1976). No equilibrium was reached between dissipating acrolein and degradation products, with the dissipating reaction apparently being continued to completion. Degradation and evaporation appear to be the major pathways for loss, while a smaller amount is lost through absorption and uptake in aquatic organisms and sediments (Bowmer and Sainty, 1977; Hopkins and Hattrup, 1974).

II. EXPOSURE

There is no available evidence that acrolein is a contaminant of potable water or water supplies (U.S. EPA, 1979).

Acrolein is a common component of food. It is commonly generated during cooking or other processing, and is sometimes produced as an unwanted

by-product in the fermentation of alcoholic beverages (Izard and Libermann, 1978; Kishi, et al. 1975; Hrdlicka and Kuca, 1965; Boyd, et al. 1965; Rosenthaler and Vegezzi, 1955). However, the data are insufficient to develop a conclusive measure of acrolein exposure from food processing or cooking.

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for acrolein to be 790 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on measured steady-state bioconcentration studies in bluegills.

Atmospheric acrolein is generated as a combustion product of fuels and of cellulosic materials (e.g., wood and cigarettes), as an intermediate in atmospheric oxidation of propylene, and as a component of the volatiles produced by heating organic substrates (U.S. EPA, 1979). Acrolein is present in urban smog; average concentrations of 0.012 - 0.018 mg acrolein/m^3 and peak concentrations of 0.030 - 0.032 mg acrolein/m^3 were noted in the air of Los Angeles (Renzetti and Bryan, 1961; Altshuller and McPherson, 1963). Diesel exhaust emissions contained 12.4 mg acrolein/m^3; trace amounts of acrolein were present in samples taken from an area of traffic; and no acrolein was detected in ambient air from an open field (sensitivity of measurement was below one part per million) (Bellar and Sigsby, 1970). Acrolein content of smoke from tobacco and marijuana cigarettes ranged from 85 to 145 ug/cigarette (Hoffman, et al. 1975; Horton and Guerin, 1974). Acrolein was detected at levels of 2.5 - 30 mg/m^3 at 15 cm above the surface of potatoes or onions cooking in edible oil (Kishi, et al. 1975).

III. PHARMACOKINETICS

A. Absorption

Total respiratory tract retention of acrolein in anesthetized dogs was 77 to 86 percent (Egle, 1972).

B. Distribution

Pertinent data were not found in the available literature.

C. Metabolism

Relatively little direct information is available on the metabolism of acrolein. In vitro, acrolein can serve as a substrate for alcohol dehydrogenases from human and horse liver (Pietruszko, et al. 1973). In vivo studies in rats indicate that a portion of subcutaneously administered acrolein is converted to 3-hydroxylpropylmercapturic acid (Kaye and Young, 1972; Kaye, 1973). Acrolein undergoes both spontaneous and enzymatically catalyzed conjugation with glutathione (Boyland and Chasseaud, 1967; Esterbauer, et al. 1975). The low pH's encountered in the upper portions of the gastrointestinal tract probably would rapidly convert acrolein to saturated alcohol compounds (primarily beta propionaldehyde) (U.S. EPA, 1979). As several of the toxic effects of acrolein are related to the high reactivity of the carbon-carbon double bond, saturation of that bond should result in detoxification (U.S. EPA, 1979).

D. Excretion

In rats given single subcutaneous injections of acrolein, 10.5 percent of the administered dose was recovered in the urine as 3-hydroxypropylmercapturic acid after 24 hours (Kaye and Young, 1972; Kaye, 1973).

IV. EFFECTS

A. Carcinogenicity

One-year and lifespan inhalation studies with hamsters indicate that acrolein is not a carcinogen or cocarcinogen (Feron and Kruysse, 1977; National Cancer Institute, 1979).

B. Mutagenicity

Both positive and negative results have been obtained in mutagenicity assays. Acrolein induced sex-linked mutations in Drosophila melanogaster (Rapoport, 1948) and was mutagenic for DNA polymerase-deficient Escherichia coli (Bilimoria, 1975) and Salmonella typhimurium (Bignami, et al. 1977). Mutagenic activity was not detected in the dominant lethal assay in ICR/Ha Swiss mice (Epstein, et al. 1972) or in a strain of E. coli used for detecting forward and reverse mutations (with or without microsomal activation) (Ellenberger and Mohn, 1976; 1977). Acrolein was weakly mutagenic for Saccharomyces cerevisiae (Izard, 1973).

C. Teratogenicity

Pertinent data were not found in the available literature.

C. Other Reproductive Effects

Exposure of male and female rats to 1.3 mg/m^3 acrolein vapor for 26 days did not have a significant effect on the number of pregnant animals or the number and mean weight of fetuses (Bouley, et al. 1976).

E. Chronic Effects

Little information is available on the chronic effects of acrolein on humans. An abstract of a Russian study indicates that occupational exposure to acrolein (0.8 to 8.2 mg/m^3), methylmercaptan (0.003 to 5.6 mg/m^3), methylmercaptopropionaldehyde (0.1 to 6.0 mg/m^3), formaldehyde (0.05 to 8.1 mg/m^3), and acetaldehyde (0.48 to 22 mg/m^3) is associated

with irritation of the mucous membranes. This effect is most frequent in women working for less than one and greater than seven years (Kantemirova, 1975). Acrolein is known to produce irritation of the eyes and nose (Albin 1962; Pattle and Cullumbine, 1956; Sim and Pattle, 1957) and is thought to be responsible, at least in part, for the irritant properties of photochemical smog (Altshuller, 1978; Schuck and Renzetti, 1960) and cigarette smoke (Weber-Tschopp, et al. 1976a; 1976b; 1977).

In the only published chronic toxicity study on acrolein in animals (Feron and Kruysse, 1977), male and female Syrian golden hamsters were exposed to acrolein at 9.2 mg/m^3 in air, seven hours per day, five days per week, for 52 weeks. During the first week only, animals evidenced signs of eye irritation, salivated, had nasal discharge, and were very restless. During the exposure period, both males and females had reduced body weight gains compared to control groups. Survival rate was unaffected. Slight hematological changes, increased hemoglobin content and packed cell volume, decreases in liver weight (-16 percent), and increases in lung weights (+32 percent) occurred only in females. In both sexes, the only pathological changes in the respiratory tract were inflammation and epithelial metaplasia in the nasal cavity.

In a study of subacute oral exposure, acrolein was added to the drinking water of male and female rats at 5 to 200 mg acrolein/l for 90 days (Newell, 1958). No hematologic, organ-weight, or pathologic changes could be attributed to acrolein ingestion.

F. Other Relevant Information

Acrolein is highly reactive with thiol groups. Cysteine and other compounds containing thiol groups antagonize the toxic effects of acrolein

(Tillian, et al. 1976; Low, et al. 1977; Sprince, et al. 1978; Munsch, et al. 1973;1974; Whitehouse and Beck, 1975). Ascorbic acid also antagonizes the toxic effects of acrolein (Sprince, et al. 1978).

The effects of acrolein, on the adrenocortical response of rats unlike those of DDT and parathion, are not inhibited by pretreatment with phenobarbital and are only partially inhibited by dexamethason (Szot and Murphy, 1970). Pretreatment of rats with acrolein significantly prolongs hexobarbital and pentobarbital sleeping time (Jaeger and Murphy, 1973).

V. AQUATIC TOXICITY

A. Acute Toxicity

A relatively narrow range of acute toxicity to six species of freshwater fish has been reported for acrolein (U.S. EPA, 1979). LC_{50} values ranged from 61 to 160 µg/l with fathead minnows, (Pimephales promelas), being most sensitive and largemouth bass, (Micropterus salmoides), the most resistant of the species tested. Results from 7 static bioassays varying from 24 to 96 hours in duration were reported. The freshwater invertebrate Daphnia magna was as sensitive to acrolein as freshwater fish with 48-hour static LC_{50} values of 59 and 80 µg/l being reported in two individual studies. The longnose killifish, (Fandulus similis), was the only marine species tested for acute toxicity of acrolein; a 48-hour flow-through LC_{50} of 150 µg/l was obtained. The eastern oyster, (Crassostrea virginica), and adult brown shrimp, (Penacus aztecus), were the most sensitive species tested an EC_{50} value of 55 µg/l based on 50% decrease in shell growth of oysters and an EC_{50} value of 100 based on loss of equilibrium of brown shrimp (Butler, 1965). Adult barnacles were more resistant in static assays with 48-hour LC_{50} values of 1,600 and 2,100 µg/l being reported.

B. Chronic Toxicity

In a chronic life cycle test with the freshwater fathead minnow, Pimephales promelas, survival of newly hatched second generation fry was reduced significantly at 42 but not 11 µg/l, leading to a chronic value of 21.8 µg/l (Macek, et al. 1976). A comparable value of 24 µg/l was obtained from reduced survival of three generations of Daphnia magna. Chronic data for marine organisms was not available.

C. Plant Effects

Pertinent data relating the phytotoxicity of freshwater marine plants could not be located in the available literature.

D. Residues

A bioconcentration factor of 344 was obtained for radio labeled acrolein administered to bluegills, (Lepomis macrochivas). A biological half-life greater than seven days was indicated (U.S. EPA. 1979).

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by the U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

Based on the use of subacute toxicological data for rats (no observable effect level of 1.56 mg/kg body weight) and an uncertainty factor of 1000, the U.S. EPA (1979) has derived a draft criterion of 6.50 µg/l for acrolein in ambient water. This draft criterion level corresponds to the calculated (U.S. EPA, 1979) acceptable daily intake of 109 µg.

The ACGIH (1977) time-weighted average TLV for acrolein is 0.1 ppm (0.25 mg/m^3). The same value is recommended by OSHA (39 FR 23540). This

standard was designed to "minimize, but not entirely prevent, irritation to all exposed individuals" (ACGIH, 1974).

The FDA permits acrolein as a slime-control substance in the manufacture of paper and paperboard for usage in food packaging (27 FR 46) and in the treatment of food starch (28 FR 2676) at not more than 0.6 percent acrolein.

B. Aquatic

The draft criterion for protecting freshwater organisms is 1.2 µg/l as a 24-hour average not to exceed 2.7 µg/l. For marine life, the draft criterion has been proposed as 0.88 µg/l, not to exceed 2.0 µg/l.

ACROLEIN

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No. 7

Acrylonitrile

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated acrylonitrile and has found sufficient evidence to indicate that this compound is carcinogenic.

ACRYLONITRILE

Summary

Acrylonitrile is the most extensively produced aliphatic nitrile and ranks 45th on the list of high-volume chemicals produced in the U.S. Chronic exposure to acrylonitrile produces mild liver damage and functional disorders of the central nervous system, cardiovascular and hemopoietic systems. Acrylonitrile has shown mutagenic activity in Drosophila and bacteria. This compound is teratogenic in rats whether exposure is by inhalation or ingestion in drinking water. There are both animal and epidemiologic data to suggest that acrylonitrile may be a human carcinogen.

The fathead minnow has an observed 96-hour LC_{50} value ranging from 10,100 to 18,100 µg/l depending on test concition and a 30-day LC_{50} value of 2,600 µg/l. For the freshwater invertebrate, Daphnia magna, a reported 48-hour LC_{50} value is 7,550 µg/l with no adverse effects to concentrations as high as 3,600 µg/l in a life cycle test. A saltwater fish has an observed 96-hour LC_{50} of 24,500 µg/l. A bluegill in a 28-day study bioconcentrated acrylonitrile 48-fold with a half-life of 4-7 days.

ACRYLONITRILE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Acrylonitrile (U.S. EPA, 1979).

Acrylonitrile (CH_2=CHCN) is an explosive, flammable liquid having a normal boiling point of 77°C and a vapor pressure of 80 mm Hg (20°C). Currently, 1.6 billion pounds per year of acrylonitrile are manufactured in the United States. The major use of acrylonitrile is in the manufacture of copolymers for the production of acrylic and modacrylic fibers. Acrylonitrile has been used as a fumigant; however, all U.S. registrations for this use were voluntarily withdrawn as of August 8, 1978 (U.S. EPA, 1979).

II. EXPOSURE

A. Water

While no data on monitoring of water supplies for the presence of acrylonitrile were found in the literature, potential problems may exist. Possible sources of acrylonitrile in the aqueous environment are: (a) dumping of chemical wastes, (b) leaching of wastes from industrial landfills, (c) leaching of monomers from polymeric acrylonitrile, and (d) precipitation from rain. Acrylonitrile is short-lived in the aqueous environment; a 10 ppm solution was completely degraded after 6 days in Mississippi River water (Midwest Research Institute, 1977).

B. Food

There is no data on the levels of acrylonitrile in food. However, acrylonitrile may contaminate food by leaching of the monomer from polyacrylonitrile containers (National Resources Defense Council, 1976). The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for

acrylonitrile to be 110 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on steady-state bioconcentration studies in bluegills.

C. Inhalation

NIOSH (1978) estimated that 125,000 workers are exposed to acrylonitrile each year. Acrylonitrile may be liberated to the atmosphere via industrial processes or by the burning of polyacrylonitrile fiber (Monsanto, 1973). Data could not be found in the available literature regarding the concentrations of acrylonitrile in ambient air.

III. PHARMACOKINETICS

A. Absorption

When orally administered to rats, essentially all of the acrylonitrile is absorbed (Young, et al. 1977).

B. Distribution

In rabbits, after administration of a 30 mg/kg dose, acrylonitrile rapidly disappeared from the blood; only 1 mg/kg remained after 4 hours (Hashimoto and Kanai, 1965). In rats the metabolites of acrylonitrile distributed to the stomach wall, erythrocytes, skin, and liver (Young, et al. 1977).

C. Metabolism

Earlier reports (Giacosa, 1883; Meurice, 1900) indicated that most aliphatic nitriles are metabolized to cyanide which is then detoxified to thiocyanate. A more recent report concluded that acrylonitrile exerts its toxicity by the metabolic release of cyanide ion, and that the relative ability of various species to convert CN^- to SCN^- determined their susceptibility to the toxic action of acrylonitrile (Brieger, et al. 1952). Other facts, however, suggest that acrylonitrile toxicity is due in part to the

acrylonitrile molecule itself or other unknown metabolite(s) rather than just to the cyanide functional group (U.S. EPA, 1979). In a comprehensive tracer study with rats Young, et al. (1977) found three uncharacterized metabolites as well as CO_2 after acrylonitrile administration. Also, cyanoethylated mercapturic acid conjugates have been detected after administration of acrylonitrile (U.S. EPA, 1979).

D. Excretion

Urinary excretion of thiocyanate after acrylonitrile administration ranges from 4-33 percent of the administered dose depending on the species (U.S. EPA, 1979). Urinary excretion also depends on route of administration (Gut, et al. 1975).

IV. EFFECTS

A. Carcinogenicity

In two studies rats received acrylonitrile in the drinking water at concentrations of 0, 35, 100 and 300 mg/l, which is equivalent to daily dosages of approximately 4, 10, 30 mg/kg body weight respectively, excess mammary tumors and tumors of the ear canal and nervous system were noted (Norris, 1977; Quast, et al. 1977). Both the intermediate and the highest doses produced increased tumor incidences. In rats administered acrylonitrile in olive oil by stomach tube at 5 mg/kg body weight 3 times per week for 52 weeks, a slight enhancement of the incidence of mammary tumors, forestomach papillomas and acanthomas, skin carcinomas, and encephalic tumors has been reported (Maltoni, et al. 1977). Also, exposure of rats by inhalation (40, 20, 10, and 5 ppm for 4 hours daily, 5 times/week) for 52 weeks caused increases in tumor incidence (Maltoni, et al. 1977). It should be pointed out that possible impurities found in the acrylonitrile used by various investigators might determine the carcinogenic effect. The specific role of these impurities has not yet been determined (U.S. EPA, 1979).

Retrospective studies on workers in a textile fiber plant (O'Berg, 1977) and on workers in the polymerization recovery and laboratory areas of a B.F. Goodrich plant (Monson, 1977) have shown higher than expected incidences of cancers of all sites in workers exposed to acrylonitrile. The greatest increase was noted with lung cancer. It should be noted that these workers were exposed to other chemicals in their working environment.

B. Mutagenicity

Acrylonitrile is a weak mutagen in Drosophila melanogaster (Benes and Sram, 1969); although toxicity limited this testing. Milvy and Wolff (1977) reported mutagenic activity for acrylonitrile in Salmonella typhimurium with a mammalian liver-activating system. In Escherichia coli mutagenic activity was observed without an activating system (Venitt, et al. 1977).

C. Teratogenicity

Studies in pregnant rats demonstrated that acrylonitrile administered by gavage at 65 mg/kg/day caused fetal malformations (Murray, et al. 1976). These malformations included acaudea, short-tail, short trunk, missing vertebrae, and right-sided aortic arch. In a subsequent study, Murray, et al. (1978) concluded that in pregnant rats exposed to 0, 40, or 80 ppm of acrylonitrile by inhalation, teratogenic effects in the offspring were seen at 80 ppm but not 40 ppm. Significant maternal toxicity was found at both 80 and 40 ppm, as well as in the previous study at 65 mg/kg/day.

D. Other Reproductive Effects

Pregnant rats receiving 500 ppm acrylonitrile in their drinking water showed reduced pup survival, possibly due to a maternal toxicity (Beliles and Mueller, 1977).

E. Chronic Toxicity

Knoblock, et al. (1972) observed a perceptible change in peripheral blood pattern, functional disorders in the respiratory and cardiovascular systems, and the excretory system, as well as signs of neuronal lesions in the central nervous system of rats and rabbits breathing acrylonitrile (50 mg/m^3 air) for 6 months. Babanov, et al. (1972) reported that inhalation of acrylonitrile vapor (0.495 mg/m^3, 5 hours/day, 6 days/week) for 6 months resulted in central nervous system disorders, increased erythrocyte count, and decreased leukocyte count in rats. Workers exposed for long periods of time to acrylonitrile have subjective complaints including headache, fatigue, nausea and weakness, as well as clinical symptoms of anemia, jaundice, conjunctivitis and abnormal values of specific gravity of whole blood, blood serum and cholinesterase values, urobilinogen, bilirubin, urinary protein and sugar (Sakarai and Kusimoto, 1972). In another study, functional disorders of the central nervous system, cardiovascular and hemopoietic systems were noted (Shustov and Mavrina, 1975). Sakarai and Kasumoto (1972) concluded that acrylonitrile exposures at levels of 5-20 ppm caused mild liver injury and probably a cumulative general toxic effect.

F. Other Relevant Information

HCN and CO were found to enhance acrylonitrile toxicity in experimental animals (Yamamoto, 1976) as well as in workers engaged in acrylonitrile production (Ostrovskaya, et al. 1976).

V. Aquatic Toxicity

A. Acute Toxicity

The 96-hour LC_{50} values of fathead minnows (Pimephales promelas) were 10,100 and 18,100 µg/l for flow-through and static tests, respectively, and 14,300 and 18,100 µg/l for hard (380 mg/l) and soft (29 mg/l) waters,

respectively (Henderson, et al. 1961). A reported 48-hour LC_{50} for Daphnia magna is 7,550 µg/l (U.S. EPA, 1978). The saltwater pinfish (Lagodon rhomboides) has an observed 96-hour LC_{50} value of 24,500 µg/l in a static concentration unmeasured test (Daugherty and Garrett, 1951).

B. Chronic Toxicity

Daphnia magna has been exposed for its life cycle and the results indicate no adverse effects at concentrations as high as 3,600 µg/l (U.S. EPA, 1978). Henderson, et al. (1961) observed a 30-day LC_{50} value of 2,600 µg/l with Pimephales promelas (fathead minnows). No chronic test data are available for saltwater species.

C. Plant Effects

Pertinent data could not be located in the available literature on the sensitivity of plants to acrylonitrile.

D. Residues

In the only reported study, the bluegill (Lepomis macrochirus) was exposed for 28 days and the determined whole body bioconcentration factor was 48, with a half-life between 4-7 days (U.S. EPA, 1978).

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

The American Conference of Governmental Industrial Hygienists threshold limit value (TLV) (ACGIH, 1974) for acrylonitrile is 20 ppm. In January, 1978, the Occupational Safety and Health Administration (OSHA) announced an emergency temporary standard for acrylonitrile of 2 ppm averaged

over an eight-hour period. Based on rat data (Norris, 1977; Quast, et al. 1977; Maltoni, et al. 1977), and using the "one-hit" model, the U.S. EPA (1979) has estimated levels of acrylonitrile in ambient water which will result in specified risk levels of human cancer:

Exposure Assumptions (per day)	Risk Levels and Corresponding Draft Criteria			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams of fish and shellfish.		0.008×10^{-4} ng/l	0.08×10^{-4} ng/l	0.8×10^{-4} ng/l
Consumption of fish and shellfish only.		0.016×10^{-4} ng/l	0.16×10^{-4} ng/l	1.6×10^{-4} ng/l

B. Aquatic

For acrylonitrile, the draft criterion to protect freshwater aquatic life is 130 µg/l as a 24-hour average, and the concentration should not exceed 300 µg/l at any time. To protect saltwater species, the draft criterion is 130 µg/l as a 24-hour average, with the concentration not to exceed 290 µg/l at any time (U.S. EPA, 1979).

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No. 8

Aldrin

Health and Environmental Effects

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APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated aldrin and has found sufficient evidence to indicate that this compound is carcinogenic.

ALDRIN

Summary

Aldrin is a man-made compound belonging to the group of cyclodiene insecticides. The chronic toxicity of low doses of aldrin include shortened lifespan, liver changes, and teratogenic effects. The induction of hepatocellular carcinoma in both male and female mice from the administration of aldrin leads to the conclusion that it is likely to be a human carcinogen. Aldrin has not been found mutagenic in several test systems although it did induce unscheduled DNA synthesis in human fibroblasts. The World Health Organization acceptable daily intake level for aldrin is 0.1 µg/kg/day.

Aldrin is rapidly converted to dieldrin by a number of fresh and saltwater species. The overall toxicity of aldrin is similar to dieldrin. The 96-hour LC_{50} values for freshwater fish vary from 2.2 to 37 µg/l with invertebrates being one order of magnitude less sensitive. Both marine fish and plants were susceptible to levels of aldrin corresponding to those of freshwater fish.

ALDRIN

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Aldrin and Dieldrin (U.S. EPA, 1979a).

Aldrin is a white crystalline substance with a melting point of 104°C. It is soluble in organic solvents. The chemical name for aldrin is 1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-1,4,:5,8-exo-dimethano-naphthalene. Aldrin is biologically altered in the environment to dieldrin, a more stable and equally toxic form. For information concerning dieldrin refer to the dieldrin hazard profile or the draft Ambient Water Quality Criteria Document for Aldrin and Dieldrin (U.S. EPA, 1979a,b).

Aldrin was primarily used as a broad spectrum insecticide until 1974 when the U.S. EPA restricted its use to termite control by direct soil injection, and non-food seed and plant treatment (U.S. EPA, 1979a). From 1966 to 1970 the use of aldrin in the United States dropped from 9.5×10^3 to 5.25×10^3 tons (U.S. EPA, 1979a). This decrease in use has been attributed primarily to increased insect resistance to aldrin and to development of substitute materials. Although the production of aldrin in the United States is restricted, formulated products containing aldrin are imported from Europe (U.S. EPA, 1979a).

II. EXPOSURE

A. Water

Aldrin has been applied to vast areas of agricultural land, and aquatic areas in the United States and in most parts of the world. As a result, this pesticide is found in most fresh and marine waters (U.S. EPA, 1979a). Levels of aldrin, ranging from 15 to 18 ng/l or as high as 407 ng/l

have been found in waters of the United States (U.S. EPA, 1976; Leichtenberg, et al. 1970). The half-life of aldrin in water one meter in depth has been estimated to be 10.1 days (MacKay and Wolkoff, 1973).

B. Food

The estimated daily dietary intake of aldrin in 16 to 19 year old males was estimated to be 0.001 mg in 1965 and only a trace amount in 1970 (Natl. Acad. Sci., 1975).

No direct measured bioconcentration factor for aldrin can be obtained because it is rapidly converted to dieldrin by aquatic organisms (U.S. EPA, 1979a). The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor of aldrin at 32. This estimate is based on the octanol/water partition coefficient for aldrin.

C. Inhalation

Aldrin enters the air through various mechanisms such as spraying, wind action, water evaporation, and adhesion to particles (U.S. EPA, 1979a). Ambient air levels of 8 ng/m^3 of aldrin have been reportec (Stanley, et al. 1971).

D. Dermal

Dermal exposure to aldrin is limited to workers employed during its manufacture and use as a pesticide. Wolfe, et al. (1972) reported that exposure in workers is mainly through dermal absorption rather than inhalation. The ban on the manufacture of aldrin in the United States has greatly reduced the risk of exposure.

III. PHARMACOKINETICS

A. Absorption

Pertinent data could not be located in the available literature concerning the absorption of aldrin (U.S. EPA, 1979a).

B. Distribution

The distribution of aldrin in humans or animals has not been extensively studied because aldrin is readily converted to dieldrin *in vivo* via epoxidation (U.S. EPA, 1979a). For example, the blood plasma levels of aldrin were lower than the corresponding blood plasma levels of dieldrin in six workers just after chronic exposure to aldrin for five weeks (Mick, et al. 1971).

C. Metabolism

The epoxidation of aldrin to dieldrin has been reported in many organisms including man (U.S. EPA, 1979a). The reaction is NADPH-dependent and the enzymes are heat-labile (Wong and Terriere, 1965). The metabolic products of aldrin include dieldrin, as well as aldrin diol, and polar metabolites excreted in the urine and feces (U.S. EPA, 1979a).

D. Excretion

Aldrin is excreted mainly in the feces and to some extent in the urine in the form of several polar metabolites (U.S. EPA, 1979a). Ludwig, et al. (1964) reported nine times as much radioactivity in the feces as in the urine of rats chronically administered ^{14}C-aldrin. A saturation level was reached in these animals and concentrations of radioactivity in the body decreased rapidly when feeding was terminated.

Specific values for the half-life of aldrin in humans were not found in the available literature. However, in humans exposed to aldrin and/or dieldrin the half-life of dieldrin in the blood was estimated to be 266 days (Jager, 1970). In another study with 12 volunteers ingesting various doses of dieldrin, Hunter, et al. (1969) estimated the average dieldrin half-life to be 369 days.

IV. EFFECTS

A. Carcinogenicity

Aldrin has induced liver tumors in males and females in various strains of mice according to reports of four separate feeding studies (Davis and Fitzhugh, 1962; Davis, 1965; 43 FR 2450; Song and Harville, 1964). According to reports of five studies in two different strains of rats, aldrin failed to induce a statistically significant carcinogenic response at all but one site (Deichmann, et al. 1967, 1970; Fitzhugh, et al. 1964; Cleveland, 1966; 43 FR 2450).

The only information concerning the carcinogenic potential of aldrin in man is an occupational study by Versteeg and Jager (1973). The workers had been employed in a plant producing aldrin and dieldrin with a mean exposure time of 6.6 years. An average time of 7.4 years had elapsed since the end of exposure. No permanent adverse effects including cancer were observed.

B. Mutagenicity

Aldrin was found not to be mutagenic in two bacterial assays (S. typhimurium and E. coli) with metabolic activation (Shirasu, et al. 1977). Aldrin did, however, produce unscheduled DNA synthesis in human fibroblasts with and without metabolic activation (Ahmed, et al. 1977).

C. Teratogenicity

Aldrin administered in single oral doses to pregnant hamsters caused significant increases in hamster fetal death and increased fetal anomalies (i.e., open eye, webbed foot, cleft palate, and others). When a similar study was done in mice at lower doses, teratogenic effects were also observed, although these effects were less pronounced (Ottolenghi, et al. 1974).

D. Other Reproductive Effects

Deichmann (1972) reported that aldrin and dieldrin (25 mg/kg diet) fed to mice for six generations affected fertility, gestation, viability, lactation and survival of the young.

E. Chronic Toxicity

The other effects produced by chronic administration of aldrin to mice, rats, and dogs include shortened lifespan, increased liver to body weight ratios, various changes in liver histology, and the induction of hepatic enzymes (U.S. EPA, 1979a).

F. Other Relevant Information

Since aldrin and dieldrin are metabolized by way of mixed function oxidase (MFO), any inducer or inhibitor of the MFO enzymes should affect the metabolism of aldrin and dieldrin (U.S. EPA, 1979a).

When aldrin is administered with DDT, or after a plateau has been reached in dogs with chronic DDT feeding, the retention of DDT by the blood and fat increases considerably (Deichmann, et al. 1969). Clark and Krieger (1976) found that tissue accumulation of ^{14}C-aldrin was significantly increased when an inhibitor of the epoxidation of aldrin to dieldrin was administered prior to ^{14}C-aldrin.

V. AQUATIC TOXICITY

A. Acute Toxicity

Aldrin is rapidly converted to dieldrin in the environment. However, a number of acute studies haved been done with aldrin, although the test concentrations have not been measured after the bioassays. Reported 96-hour static LC_{50} values are as follows: bluegill (Lepomis macrochirus) 4.6 to 15 µg/l (Henderson, et al. 1959; Macek, et al. 1969); rainbow trout (Salmo gairdneri) 2.2 to 17.7 µg/l (Macek, et al. 1969; Katz, 1961); and

fathead minnows (Pimephales promelas) 32 and 37 µg/l (Henderson, et al. 1959). Acute toxicity varies greatly in freshwater invertebrates. In bioassays in which the aldrin concentrations were not measured, the observed 48-hour LC_{50} value for Daphnia pulex was 28 µg/l (Sanders and Cope, 1966), and the observed 96-hour LC_{50} values ranged from 4,300 to 38,500 µg/l for scud, Gammarus spp. (Sanders, 1969, 1972; Gaufin, et al. 1965).

In flow-through exposures to aldrin, the 48 and 96-hour LC_{50} values for six saltwater fish species ranged from 2.0 to 7.2 µg/l. Invertebrate LC_{50} values ranged from 0.37 to 33.0 µg/l (U.S. EPA, 1979a).

B. Chronic Toxicity

No entire cycle or embryo-larval tests have been reported for any fresh or saltwater species (U.S. EPA, 1979a).

C. Plant Effects

An aldrin concentration of 10,000 µg/l reduced the population growth in 12 days for water meal, Wolffia papulifera (Worthley and Schott, 1971). The productivity of a phytoplankton community was reduced 85 percent after four hour exposure to 1,000 µg/l aldrin (Butler, 1963).

D. Residues

No freshwater or saltwater residue studies have been reported for aldrin (U.S. EPA, 1979a).

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

The current exposure level for aldrin set by the Occupational Safety and Health Administration is a time-weighted average of 250 $\mu g/m^3$ for skin absorption (37 FR 22139). In 1969, the U.S. Public Health Service Advisory Committee recommended that the drinking water standard for aldrin be 17 µg/l (Mrak, 1969). The U.N. Food and Agricultural Organization/World Health Organization acceptable daily intake for aldrin is 0.1 µg/kg/day (Mrak, 1969).

The carcinogenicity data of the National Cancer Institute (1976) (43 FR 2450) were used to calculate the draft water quality criterion for aldrin which keeps the lifetime cancer risk for humans below 10^{-5}. The concentration for aldrin is 4.6×10^{-2} ng/l (U.S. EPA, 1979a).

B. Aquatic

Draft criterion has not been proposed directly for aldrin because of its rapid conversion to dieldrin (U.S. EPA, 1979a).

ALDRIN

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No. 9

Allyl Alcohol

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

ALLYL ALCOHOL

Summary

Allyl alcohol is a severe irritant to the mucous membranes at high concentrations. Hepatotoxicity has been seen after oral and inhalation exposures, however, results indicate that this effect may not be cumulative. Allyl alcohol is also absorbed percutaneously.

Information on the carcinogenic, mutagenic, teratogenic or other reproductive effects of allyl alcohol was not found in the available literature.

Data concerning the effects of allyl alcohol to aquatic organisms were not found in the available literature.

I. INTRODUCTION

This profile is based on computerized searches of Toxline, Biosis and Chemical Abstracts, and a review of other available appropriate information sources as available.

Allyl alcohol (molecular weight-58.08) is a limpid liquid with pungent odor. It is soluble in water, alcohol and ether, has a melting point of -50°C and a boiling point of 96-97°C (Sax, 1979).

The major uses of allyl alcohol are in the manufacture of allyl compounds, war gas, resins, and plasticizers (Windholz, 1976). Sixty kt. are used in this country per year, of which 50 kt. are used to manufacture glycerol (Kirk and Othmer, 1963).

After several years of storage, allyl alcohol polymerizes into a substance that is soluble in chloroform but not water. When treated with ether this substance becomes brittle (Windholz, 1976).

II. EXPOSURE

Pertinent data were not found in the available literature on air or water exposure.

Esters of allyl alcohol are used as food flavorings. Natural derivatives of allyl alcohol are widely distributed in vegetable material (Lake, et al. 1978).

III. PHARMACOKINETICS

A. Absorption and Distribution

Pertinent data were not found in the available literature.

B. Metabolism

It has been suggested that allyl alcohol is completely metabolized and that acrolein might be an intermediate metabolite (Browning, 1965). The rate of metabolism in rats was found to be about 23 mg/kg/hr. during constant intravenous infusion (Carpanini, et al. 1978).

C. Excretion

Allyl alcohol was not found in the urine of animals that had been dosed subcutaneously or intravenously with the compound (Browning, 1965). Other pertinent data were not found in the available literature.

IV. EFFECTS

A. Carcinogenicity, Mutagenicity, Teratogenicity, and Reproductive Effects

Information on the carcinogenic effects of allyl alcohol was not found in the available literature.

B. Chronic Toxicity

Lake, et al. (1978) administered allyl alcohol to rats by gastric intubation. The rats were dosed daily for 1, 10, or 28 days. Liver homogenates from treated animals were analyzed for enzyme activity. Administration for one day produced marked periportal necrosis, but repeated administration for 10 or 28 days did not seem to increase the damage.

Allyl alcohol administration in the drinking water at a dose of 72 mg/kg/day caused weight loss, transient pulmonary rales, crustiness of the eyelids, and local areas of liver necrosis (Browning, 1965).

Rats exposed to 40, 60, or 100 ppm of allyl alcohol by inhalation showed signs of acute mucous membrane irritation, such as gasping and nasal discharge. At the 100 ppm dose, the animals died after 10 exposures (Browning, 1965). No gross toxicity was seen at 5 or 10 ppm, 5 days a week for 13 months in rats, rabbits, guinea pigs, and dogs. However, mild reversible degenerative changes in the liver and kidney were seen at the seven ppm dose. A dose of 50 ppm was lethal to rats after 30 days (Torkelson, et al. 1959).

Carpanini, et al. (1978) gave rats doses of allyl alcohol 50, 100, 200, or 800 ppm im the drinking water for 15 weeks. Weight loss was seen in males given 100, 200, or 800 ppm and females given 800 ppm. Food consumption values were lower than the controls in males at 200 ppm and 800 ppm and females at 800 ppm. A dose-related decrease in water consumption was seen in all treated animals. Minor changes were seen in the liver, kidneys, and lungs of both treated and control groups upon histological examination.

C. Acute Toxicity

Oral LD_{50}'s of allyl alcohol have been found to be 64-100 mg/kg for rats, 96-139 mg/kg for mice, and 52-71 mg/kg for rabbits; 43 mg/kg was lethal to dogs. Intraperitoneal LD_{50}'s were 42 mg/kg for rats and 60 mg/kg for mice. In rabbits an LD_{50} of 53-89 mg/kg was found by percutan- eous absorption (Carpanini, et al. 1978). Inhalation of 1000 ppm was lethal to rabbits and monkeys after 3 to 4 hours. Erythema of the conjunctiva and swelling of the cornea are seen in the eye after exposure to allyl alcohol, however, no permanent damage was noted. Application to the skin caused only mild erythema. Intravenous injection produced a drop in blood pressure. Injection of 40 minims in a 20 percent saline solution caused fluctuations in the blood pressure, of rabbits resulting in violent convulsions. Vomiting, diarrhea, convulsions, apathy, ataxia, lacrimation and coma are seen after oral administration. Few cases of serious injury due to inhalation have been reported, however, because concentrations that would cause severe damage in a short period of time are painful to the eyes and nose. Five ppm are detectable by irritation and 2 ppm by odor (Browning, 1965).

Moderate air contamination has been found to cause lacrimation, pain around the eyes and blurred vision in man lasting up to 48 hours (Carpanini, et al. 1978).

D. Other Relevant Information

Allyl alcohol has an unusual effect on the central nervous system of mice and rats. The effect is seen as apathy, unwillingness to move, anxiety, and no interest in escaping. It is apparently different from narcosis seen with other agents (Dunlap, et al. 1958).

V. AQUATIC TOXICITY

Pertinent data were not found in the available literature.

VI. EXISTING GUIDELINES

The recommended maximum atmospheric concentration (8 hours) is 2 ppm (Indust. Hyg. Assoc., 1963).

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No. 10

Antimony

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

10-I

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

ANTIMONY

Summary

The adverse health effects most commonly associated with exposure to antimony are pulmonary, cardiovascular, dermal, and certain effects on reproduction, development, and longevity. Cardiovascular changes have been well-established with exposure to antimony and probably represent the most serious threat to human health. Antimony has not been associated with carcinogenic effects. The lowest observed effect level for antimony in the drinking water of rats was 5 ppm. A draft criterion of 145 µg/l has been recommended for antimony in water based on an acceptable daily intake of antimony from water, fish, and shellfish for man of 294 µg.

Antimony is highly toxic to aquatic organisms at a concentration ranging from 19 mg/l to 530 mg/l. Chronic values for antimony in freshwater organisms range from 0.8 mg/l to 5.4 mg/l.

ANTIMONY

I. INTRODUCTION

This profile is based primarily on the Ambient Water Quality Criteria Document for Antimony (U.S. EPA, 1979). The health hazards of antimony and its compounds have also been recently reviewed by the National Institute for Occupational Safety and Health (NIOSH, 1978).

Antimony (Sb; molecular weight 121.8) is a silvery, brittle, solid belonging to group VB of the periodic table and lies between arsenic and bismuth. It is classified as both a metal and a metalloid, and its principal oxidation states are +3 and +5. Antimony has a boiling point of 1366°C and a melting point of 636°C. Most inorganic compounds of antimony are either only slightly water soluble or decompose in aqueous media.

Antimony reacts with both sulfur and chlorine to form the tri-and pentavalent sulfides and chlorides. Oxidation to antimony trioxide (stibine), the major commercial oxide of antimony, is achieved under controlled conditions.

Consumption of antimony in the United States is on the order of 40,000 metric tons per year (Callaway, 1969), of which half is obtained from recycled scrap and the balance mainly imported. Use of antimony in the United States is directed chiefly to the manufacture of ammunition, storage batteries, matches and fireworks, and in the fire-proofing of textiles.

II. EXPOSURE

A. Water

Schroeder (1966) compiled data from surveys of municipal water supplies in 94 cities and reported that levels averaged less than 0.2 µg/l in finished water. In a related study, Schroeder and Kraemer (1974) noted that tap water levels of antimony can be elevated in soft water supplies due to leaching from plumbing.

B. Food

Because of the wide range of antimony levels in various types of foods, it is not possible to accurately estimate an average dietary intake. Tanner and Friedman (1977) concluded that dietary intake of antimony is negligible, based upon trace metal food monitoring data from the U.S. Food and Drug Administration. However, in earlier studies, calculated average dietary intakes were reported at 100 µg per day for man (Schroeder, 1970) and in the range of 0.25 to 1.28 mg per day for institutionalized children (Murthy, et al. 1971). In one study on antimony levels in Italian diets a mean daily value of several micrograms was reported (Clemente, 1976).

C. Inhalation

Antimony is not generally found in ambient air at measurable concentrations. National Air Sampling Network data for 1966 showed possibly significant levels at only four urban stations (0.042 to 0.085 $\mu g/m^3$) (Schroeder, 1970; Woolrich, 1973).

D. Other Routes

The total body burden of antimony arising from all environmental media is apparently very small relative to other trace metals (i.e., lead, mercury, cadmium) in the environment. Clemente (1976) published

limited data on fecal and urinary levels of antimony in selected Italian populations and concluded that daily intakes were less than 2.0 µg/day. In addition, data on the bioconcentration potential of antimony in fish (U.S. EPA, 1978) indicate that no bioaccumulation is likely to occur. The U.S. EPA (1979) has calculated the weighted average bioconcentration factor (BCF) for antimony to be 1.4 for the edible portions of fish and shellfish consumed by Americans. This estimate was based on 25-day bioconcentration studies in bluegill.

III. PHARMACOKINETICS

Absorption of antimony in man and animals is mainly via the respiratory and gastro-intestinal tracts. The extent of absorption is dependent on factors such as solubility, particle size, and chemical forms (Felicetti, et al. 1974a; 1974b). Absorption via the GI tract is of the order of several percent with antimony trioxide, a relatively insoluble compound , and presumably would be much greater with soluble antimonials.

Blood is the main carrier for antimony, the extent of partition between blood compartments depending on the valence state of the element and the animal species studied (Felicetti, et al. 1974a). The rodent exclusively tends to concentrate trivalent antimony for long periods in the erythrocyte (Djuric, et al. 1962). Whatever the species, it can generally be said that pentavalent antimony is borne by plasma and trivalent antimony in the erythrocyte. Clearance of antimony from blood to tissues is relatively rapid, and this is especially true in the case of parenteral administration and the use of pentavalent antimony (Casals, 1972; Abdalla and Saif, 1962; El-Bassouri, et al. 1963).

The tissue distribution and subsequent excretion of antimony is a function of the valence state.

In animals, trivalent antimony aerosols lead to highest levels in the lung, skeleton, liver, pelt, and thyroid while pentavalent aerosols show a similar distribution, with the exception of slower uptake by the liver (Felicetti, et al. 1974a; 1974b; Thomas, et al. 1973).

Parenteral administration to animals shows trivalent antimony accumulating in the liver and kidney as well as in pelt and thyroid (Molkhia and Smith, 1969; Waitz, et al. 1965).

In man, non-occupational or non-therapeutic exposure shows very low antimony levels in various tissues with little evidence of accumulation (Abdalla and Saif, 1962). Chemotherapeutic use leads to highest accumulation in liver, thyroid, and heart for trivalent antimony.

The biological half-life of antimony in man and animals is a function of route of exposure, chemical form, and oxidation state. The rat appears to be unique in demonstrating a long biological half-time owing to antimony accumulation in the erythrocyte. In other species, including man, moderate half-times of the order of days have been demonstrated. While most soft tissues do not appear to accumulate antimony, the skin does show accumulation, perhaps because of its high content of sulfhydryl groups. With respect to excretion, injection of trivalent antimony leads mainly to urinary excretion in guinea pigs and dogs, and mainly fecal clearance in hamsters, mice and rats.

Pentavalent antimony is mainly excreted via the kidney in most species owing to its higher levels in plasma.

Unexposed humans excrete less than 1.0 µg antimony daily via urine, while occupational or clinical exposure may result in markedly increased amounts.

IV. EFFECTS

A. Carcinogenicity

Antimony has not been tested for carcinogenic activity using an appropriately designed chronic bioassay protocol. However, Shroeder (1970) indicated that the chronic administration of antimony at 5 ppm in the drinking water of rats, had no apparent tumorigenic effect. However, the shortened life span of treated animals (average 106 to 107 days less than controls) limits the usefulness of these data. Similar results were also observed in a study with mice chronically exposed to antimony at 5 ppm in the drinking water (Kanisawa and Schroeder, 1969).

A single epidemiologic investigation has been conducted into the role of antimony in the development of occupational lung cancer (Davies, 1973). This retrospective study, which was limited in scope, provided no definitive information to support the possible role of antimony in lung cancer development.

B. Mutagenicity

Antimony has not been tested for activity in standard mutagenicity bioassays.

C. Teratogenicity

Little information is available concerning possible teratogenic effects of antimony. In one study, Casals (1972) observed no effects, i.e., no fetal abnormalities, following administration of a solution of antimony dextran glycoside containing 125 or 250 mg Sb/kg to pregnant rats on days 8 to 15 of gestation.

D. Other Reproductive Effects

Aiello (1955) observed a higher rate of premature deliveries among female workers engaged in antimony smelting and processing. In

addition, dysmenorrhea was frequently reported among women workers. Similarly, Belyaeva (1967) reported that a greater incidence of gynecological disorders was found among antimony smelter workers than in a control group (77.5 percent vs. 56 percent; significance unknown). Spontaneous late abortions occurred in 12 percent of the exposed females compared to 4.1 percent among controls. Average urine levels of antimony for exposed workers, however, were extremely high, ranging from 2.1 to 2.9 mg/100 ml. Antimony was also found in breast milk (3.3$\pm$ 2 mg/10), placental tissue (3.2 to 12.6 mg/100 mg), amniotic fluid (6.2 to 2.8 mg/100 mg), and umbilical cord blood (6.3 $\pm$ 3 mg/100 ml).

In studies with rats exposed either to antimony dust (50 mg/kg, i.p.) or to antimony trioxide dust (250 mg/m^3, 4 hours per day for 1.5 to 2 months), Belyaeva (1967) reported increased reproductive failure, fewer offspring, and damage to the reproductive tissues (ovary and uterus).

E. Chronic Toxicity

The toxic effects of exposure to antimony have been repeatedly observed in both humans and experimental rodents. Pulmonary, cardiovascular, dermal, and certain effects on reproduction, development, and longevity are among the health effects most commonly associated with antimony exposure.

Cardiovascular changes have been well established following exposure to antimony and probably represent the most serious human health effects demonstrated thus far (U.S. EPA, 1979). Air concentrations of

antimony trisulfide exceeding 3 mg/cu m were associated with the induction of altered ECG patterns and some deaths attributed to myocardial damage among certain antimony workers (Brieger, et al. 1954). Also, in parallel studies on animals, Brieger and coworkers (1954) observed ECG alterations in rats and rabbits exposed to antimony in air at levels of 3.1 to 5.6 mg/m^3, 7 hours/day, 5 days/week for at least 6 weeks.

Gross and coworkers (1955) presented evidence for growth retardation occurring when rats were chronically fed diets containing two percent antimony trioxide. Other investigators (Schroeder, et al. 1970; Kanisawa and Schroeder, 1969) reported that oral exposure to 5 ppm of antimony in drinking water had no effect on the rate of growth of either rats or mice. However, the 5 ppm exposure level was effective in producing slight but significant lifespan shortening in both rats and mice, and altered blood chemistries in exposed rats. Therefore, the 5ppm exposure level has been considered the "lowest observed effect level" in animals that likely approximates the "no effect" level for antimony-induced effects on growth and longevity.

V. AQUATIC TOXICITY

A. Acute Toxicity

The data base for antimony and freshwater organisms is small and indicates that plants may be more sensitive than fish or invertebrate species.

A 96-hour LC_{50} of 22,000 µg/l was reported for antimony trichloride with the fathead minnow, whereas the value for bluegills and antimony trioxide is above 530,000 µg/l (U.S. EPA, 1979). For Daphnia magna a 48-hour LC_{50} value of 19,000 µg/l and a 64-hour EC_{50} value of 19,800 µg/l have been reported for antimony trichloride. Another 48-hour

EC_{50} value for antimony trioxide and Daphnia magna has been reported to be above 530,000 µg/l (U.S. EPA, 1979).

B. Chronic Toxicity

No adverse effects on the fathead minnow were observed during an embryo-larval test with antimony trioxide at the highest test concentration of 7.5 µg/l (U.S. EPA, 1978). However, a comparable test with antimony trichloride produced limits of 1,100 and 2,300 µg/l for a chronic value of 800 µg/l. A life cycle test with Daphnia magna and antimony trichloride produced limits of 4,200 and 7,000 µg/l for a chronic value of 5,400 µg/l (U.S. EPA, 1979). Pertinent information could not be located in the available literature regarding chronic effects of antimony on saltwater organisms.

C. Plants Effects

The 96-hour EC_{50} values for chlorophyll a inhibition and reduction in cell number of the freshwater alga, Selenastrum capricornutum are 610 and 630 µg/l, respectively. This indicates that aquatic plants may be more sensitive than fish or invertebrate species (U.S. EPA, 1978). No inhibition of chlorophyll a reduction or in cell numbers of the marine alga, Skeletonema costatum, were observed at concentrations as high as 4,200 µg/l (U.S. EPA, 1978).

D. Residues

There was no bioconcentration of antimony by the bluegill above control concentrations during a 28 day exposure to antimony. No data have been reported on bioconcentration of antimony in marine species.

VI EXISTING GUIDELINES AND STANDARDS

Neither the human health nor aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of

public review; therefore, there is a possibility that these criteria may be changed.

A. Human

Existing occupational standards for exposure to antimony are reviewed in the recently released NIOSH criteria document, Occupational Exposure to Antimony (U.S. Department of Health, Education and Welfare, 1978). As stated in the NIOSH (1978) document, the American Conference of Governmental Industrial Hygienists (ACGIH), in 1977, listed the TLV for antimony as 0.5 mg/m^3 along with a notice of intended change to a proposed TLV of 2.0 mg/m^3 for soluble antimony salts. The proposed TLV was based mainly on the reports of Taylor (1966) and Cordasco (1974) on accidental poisoning by antimony trichloride and pentachloride, respectively. Proposed limits of 0.5 mg/m^3 for handling and use of antimony trioxide and 0.05 mg/m^3 for antimony trioxide production were included in the ACGIH (1977) notice of intended changes.

The Occupational Safety and Health Administration earlier adopted the 1968 ACGIH TLV for antimony of 0.5 mg/m^3 as the Federal standard (29 CFR 1910.1000). This limit is consistent with limits adopted by many other countries as described in Occupational Exposure Limits for Airborne Toxic Substances - A tabular Compilation of Values from Selected Countries, a publication released by the International Labour Office in 1977. The NIOSH (1978) document also presented table of exposure limits from several countries, reproduced here as Table 1; the typical standard adopted was 0.5 mg/m^3.

TABLE 1

HYGIENIC STANDARDS OF SEVERAL COUNTRIES FOR
ANTIMONY AND COMPOUNDS IN THE WORKING ENVIRONMENT

Country	Standard (mg/m^3)	Qualifications
Finland	0.5	Not stated
Federal Republic of Germany	0.5	8-hour TWA
Democratic Republic of Germany	0.5	Not stated
Rumania	0.5	Not stated
USSR	0.5	For antimony dust
	0.3	For fluorides and chlorides (tri-and pentavalent); obligatory control of HF and HCl
	1.0	For trivalent oxides and sulfides
	1.0	For pentavalent oxides and sulfides
Sweden	0.5	Not stated
USA 8-hour TWA		0.5
Yugoslavia	0.5	Not stated

Modified from Occupational Exposure Limits in Airborne Toxic Substances, International Labour Office.

The 0.5 mg/m^3 level was also recommended as the United States occupational exposure standard by the NIOSH (1978) criteria document, based mainly on estimated no-effect levels for cardiotoxic and pulmonary effects.

Based upon the data presented in the Ambient Water Quality Criteria Document for Antimony (U.S. EPA, 1979), a recommended draft criterion of 145 µg/l has been established. This value is based upon an acceptable daily intake for man of 294 ug, derived from experimental animal studies in which 5 ppm of antimony produced a slight shortening of lifespan with no other deserved effects. An uncertainty factor of 100 was used in extrapolating from animal data to human health effects.

B. Aquatic

The draft criterion for Antimony to protect freshwater aquatic life as derived using the Guidelines is 120 µg/l as a 24 hour average and the concentration should not exceed 1,000 µg/l at any time.

A saltwater criterion was not derived (U.S. EPA, 1979)

ANTIMONY

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No. 11

Arsenic

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated arsenic and has found sufficient evidence to indicate that this compound is carcinogenic.

ARSENIC

SUMMARY

Epidemiological studies have shown increased death rates from lung cancer in workers exposed to arsenic, probably through inhalation. Other human studies have shown increased skin cancers in non-occupationally exposed populations. Increased incidence of lymphomas and hemangioendotheliomas are also occasionally reported.

Arsenicals have produced mutagenic effects in plants, bacteria, *in vitro* leukocyte cultures, and in the lymphocytes of exposed humans. The teratogenic effects of arsenicals have been demonstrated in many animal species. An increased frequency of abortions in pregnant women exposed to arsenic has been reported in a single study (U.S. EPA, 1979).

The chronic toxic effects of arsenic involve skin hyperkeratosis, liver damage, neurological disturbances (including hearing loss), and a gangrenous condition of the extremities (Blackfoot disease). An increased mortality from cardiovascular disease resulting from chronic arsenic exposure has been suggested in two studies.

The data base for the toxicity of arsenic to aquatic organisms is more complete for freshwater organisms, where concentrations as low as 128 µg/l have been acutely toxic to freshwater fish. A single marine species produced an acute value in excess of 8,000 µg/l. Based on one chronic life cycle test using *Daphnia magna*, a chronic value for arsenic was estimated at 853 µg/l.

ARSENIC

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Arsenic (U.S. EPA, 1979).

Arsenic is a gray, crystalline metalloid with a molecular weight of 74.92, a density of 5,727, a melting point (at 28 atmospheres) of 817°C, and a boiling point (sublimates) of 613°C (Weast, 1975). Arsenic exists in a variety of valence states; the most common forms include pentavalent (arsenate), trivalent (arsenite), and -3 valency (arsine). Properties of some inorganic arsenic compounds are shown in Table 1.

Conditions of low pH, low oxidation-reduction potential, and low dissolved oxygen in water favor formation of the lower valency states (arsenite and arsine); more basic, oxygenated waters favor the presence of arsenate. Inorganic arsenic can be converted to organic alkyl-arsenic acids and to methylated arsines under both aerobic and anaerobic conditions (U.S. EPA, 1979).

Arsenic and its compounds are used in the manufacture of glass, cloth, and electrical semiconductors, as fungicides and wood preservatives, as growth stimulants for plants and animals, and in veterinary applications (U.S. EPA, 1976).

Production is currently 1.8×10^4 metric tons per year (U.S. EPA, 1979).

Arsenic will persist in some form in the environment. Inorganic arsenate is thermodynamically favored under normal conditions over arsenite in water and is a more soluble form (Ferguson and Gavis, 1972). Both arsenate and arsenite may be precipitated from water by adsorption onto iron and alum-

Table 1. Properties of Some Inorganic Arsenic Compounds
(Standen, 1967; U.S. EPA, 1976)

Compound	Formula	Water Solubility	Specific Properties
Arsenic trioxide	As_2O_3	12×10^6 µg/l @ 0°C 21×10^6 µg/l @ 25°C	Dissolves in water to form arsenious acid (H_3AsO_3: $K = 8 \times 10^{-10}$ @ 25°C)
Arsenic pentoxide	As_2O_5	2300×10^6 µg/l @ 20°C	Dissolves in water to form arsenic acid (H_3AsO_4: $K_1 = 2.5\ 10^{-4}$ $K_2 = 5.6 \times 10^{-8}$; $K_3 = 3 \times 10^{-13}$)
Arsenic hydride	AsH_3	20 ml/100 g cold water	This compound and its methyl derivatives are considered to be the most toxic.
Arsenic(III) sulfide	As_4S_6	520 µg/l @ 18°C	Burns in air forming arsenic trioxide and sulfur dioxide; occurs naturally as orpiment.
Arsenic sulfide	As_4S_4		Occurs naturally as realgar.
Arsenic(V) sulfide	As_4S_{10}	1400 µg/l @ 0°C	

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inum compounds (U.S. EPA, 1979). Methylated arsines appear to be volatile and sparingly soluble. Waters containing high organic matter may bind arsenic compounds to colloidal humic matter (U.S. EPA, 1979).

II. EXPOSURE

Arsenic appears to be ubiquitous in the environment. The earth's crust contains an average arsenic concentration of 5 mg/kg (U.S. EPA, 1976). The major sources of arsenic in the environment are industrial, such as those in the smelting of non-ferrous ores and in coal-fired power plants that utilize fuel containing arsenic. Substantial arsenic contamination of water can occur from the improper use of arsenical pesticides (U.S. EPA, 1979).

Based on available monitoring data, the U.S. EPA (1979) has estimated the uptake of arsenic by adult humans from air, water, and food:

Source	mg/day	
	Maximum Conditions	Minimum Conditions
Atmosphere	.125	.001
Water	4.9	0.002
Food Supply	.9	.007
Total	5.925	.010

Contaminated well water, seafood, and air near smelting plants all present sources of high potential arsenic intake.

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor (BCF) for arsenic to be 2.3 in the edible portions of fish and shellfish consumed by Americans. This estimate was based on bioconcentration studies in freshwater fish.

III. PHARMACOKINETICS

A. Absorption

The main routes by which arsenic can enter the body are inhalation and ingestion. Particle size and solubility greatly influence the biological fate of inhaled arsenic. Falk and Kotin (1961) have reported that the optimal range of particle size for deposition in the lower tracheobronchial tree is 0.1 to 2 μ. Larger particles are trapped by the mucous membranes of the nose and throat and swallowed; following this, the particles may be absorbed from the gastrointestinal tract (U.S. EPA, 1979).

Human inhalation studies in terminal lung cancer patients (Holland, et al. 1959) have indicated that 4.8 to 8.8 percent of inhaled arsenic-74 in cigarette smoke may be absorbed. Radioactive arsenite inhaled in an aerosol solution by two patients showed 32 and 62 percent absorption, respectively. Pinto, et al. (1976) studied arsenic excretion in 24 workers exposed to the compound during copper smelting; urinary arsenic levels were found to correlate significantly with average airborne arsenic concentrations.

Water soluble arsenicals are readily absorbed through the gastrointestinal tract. Studies with radioactive arsenate administered orally to rats have shown 70 to 90 percent absorption from the gastrointestinal tract (Urakubo, et al. 1975; Dutkiewicz, 1977). Arsenic trioxide is only slightly soluble in water and is not well absorbed. Theoretically, trivalent arsenicals should be less readily absorbed than pentavalent forms due to reactivity with membrane components

and lower solubility (U.S. EPA, 1979). However, investigators have reported high absorption of trivalent arsenic from the gastrointestinal tract in humans (Bettley and O'Shea, 1975; Crecelius, 1977).

The absorption of arsenicals following dermal exposure has been described in rats (Dutkiewicz, 1977) and humans (Robinson, 1975; Garb and Hine, 1977).

Arsenic has been detected in the tissues (Kadowaki, 1960) and cord blood of newborns (Kagey, et al. 1977), and thus transfers across the placenta in humans.

B. Distribution

Injection of radiolabelled arsenite in terminally ill patients produced widespread distribution of the compound (WHO, 1973). Hunter, et al. (1942) studied the distribution of radioactive arsenicals in humans following oral and parenteral administration and found arsenic in the liver, kidney, lungs, spleen, and skin during the first 24 hours after administration. Levels of arsenic are maintained for long periods in bone, hair and nails (Kadowaki, 1960; Liebscher and Smith, 1968).

Tissue distribution of pentavalent arsenic has been described in only a few animal studies; these studies indicate only minor differences in distribution between trivalent and pentavalent arsenicals (WHO, 1973).

C. Metabolism

Studies with brain tumor patients given injections of trivalent arsenic indicate that about 60 percent of the total urinary arsenic was in the pentavalent state the first day after dosing (Mealey, et al. 1959). Braman and Foreback (1973) have analyzed human urine samples and detected high amounts of methylated forms (dimethyl arsenic acid and methyl arsenic acid). Analysis of the urine of one patient who ingested arsenic-contaminated wine indicated that 8 percent of the initial dose was excreted as inorganic arsenic, 50 percent was excreted as dimethyl arsenic acid, and 14 percent was excreted as methyl arsenic acid (Crecelius, 1977).

The half-lives of inorganic and organic (methylated) arsenicals in one patient have been reported as 10 and 30 hours, respectively (Crecelius, 1977).

D. Excretion

Arsenic is excreted primarily in the urine, with small amounts removed in the feces and through normal hair loss and skin shedding (U.S. EPA, 1979). Reports of minor arsenic loss in sweat have also been made (Vellar, 1969).

Small amounts of radioactive arsenic (.003 to .35 percent) have been detected in expired air following administration to rats (Dutkiewicz, 1977) and chickens (Overby and Fredrickson, 1963).

IV. EFFECTS

A. Carcinogenicity

Epidemiological studies have shown an increased mortality rate from respiratory cancer in workers exposed to

arsenic during smelting operations (Lee and Fraumani, 1969; Pinto and Bennett, 1963; Snegireff and Lombard, 1951; Kuratsune, et al. 1974). A retrospective study of Dow Chemical employees indicated that workers exposed primarily to lead arsenate and calcium arsenate showed increased death rates from lung cancer and malignant neoplasms of the lymphatic and hematopoietic systems (except leukemia) (Ott, et al. 1974).

A similar trend was noted in a study of retired Allied Chemical workers (Baetjer, et al. 1975).

High rates of development of skin cancers have been reported in several studies of populations exposed to high concentrations of arsenic in drinking water (Geyer, 1898; Bergogilio, 1964; Tseng, et al. 1968).

Hemangioendothelioma of the liver associated with exposure to arsenicals through ingestion has been reported in several case studies (Roth, 1957; Regelson, et al. 1968).

Extensive experiments in animal systems with arsenicals administered in the diet or drinking water, or applied topically or by intratracheal instillation failed to show positive tumorigenic effects (U.S. EPA, 1979). However, two recent reports have shown effects in animals. Schrauzer and Ishmael (1974) indicated that feeding of sodium arsenite in drinking water accelerated the rate of spontaneous mammary tumor formation. Osswald and Goerttler (1971) found an increase in leukemias and lymphomas in mice injected repeatedly with sodium arsenate.

Animal studies on the skin tumor-promoting or co-carcinogenic effects of arsenicals have produced negative results (Raposo, 1928; Baroni, et al. 1963; Boutwell, 1963).

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B. Mutagenicity

An increased incidence of chromosomal aberrations has been found in persons exposed to arsenic occupationally and medically (Petres, et al. 1970; Nordenson, et al. 1978; Burgdorf, et al. 1977).

In vitro chromosomal changes following exposure to arsenicals have been reported in root meristem cultures (Levan, 1945) and in human leukocyte cultures (Petres and Hundeiker, 1968; Petres, et al. 1970, 1972; Paton and Allison, 1972).

Arsenate has been found to increase the frequency of chromosome exchanges in Drosophila. Several organic arsenicals have a synergistic effect with ethylmethane sulfonate in producing chromosome abnormalities in barley (Moutshcen and Degraeve, 1965).

Sodium arsenate, sodium arsenite, and arsenic trichloride produced positive mutagenic effects in a recombinant strain of Bacillus subtillus (Nishioka, 1975). Loforth and Ames (1978) were unable to show mutagenic effects of trivalent and pentavelent arsenicals in the Ames Salmonella assay. Arsenite exposure decreased the survival of E. coli after UV damage of cellular DNA (Rossman, et al. 1975).

C. Teratogenicity

Nordstrom, et al. (1978) have reported an increase in the frequency of spontaneous abortions in pregnant women living in the vicinity of a copper smelting plant; the exposure environment was complex, involving several heavy metals and sulfur dioxide.

Sodium arsenate has been shown to induce teratogenic effects in the chick embryo (Ridgway and Karnofsky, 1952), in golden hamsters (Ferm and Carpenter, 1968; Ferm, et al. 1971), in mice (Hood and Bishop, 1972), and rats (Beaudoin, 1974). Malformations noted included exencephaly, anencephaly, renal agenesis, gonadal agenesis, eye defects, and rib and genitourinary abnormalities. Sodium arsenite injected intraperitoneally into mice produced a lower incidence of malformations than an equivalent dose of sodium arsenate (Hood and Bishop, 1972; Hood, et al. 1977). Thacker, et al. (1977) has noted that a higher oral dose of sodium arsenate is needed to produce teratogenic effects in mice, when compared to intraperitoneal doses.

Feeding of three generations of mice with low doses of sodium arsenite in the chow failed to produce teratogenic effects, but did decrease litter size (Schroeder and Mitchener, 1971).

D. Other Reproductive Effects

Pertinent information could not be located in the available literature regarding other reproductive effects.

E. Chronic Toxicity

A variety of chronic effects of arsenic exposure has been noted. This includes a characteristic palmar-

plantar hyperkeratosis and a gangrenous condition of the hands and feet called Blackfoot disease (U.S. EPA, 1979). Several clinical reports of liver damage in patients treated with arsenical medication have been published (WHO, 1979). An increased mortality from cardiovascular disease has been noted in two epidemiological studies of smelter workers exposed to high airborne arsenic (Lee and Fraumeni, 1969; U.S. EPA, 1979). Neurological disturbances, including hearing loss, in workers exposed to arsenicals have been reported (WHO, 1979).

Effects of arsenicals on the hematopoietic system following chronic exposure have also been noted (WHO, 1979). These include disturbed erythropoiesis and granulocytopenia, which may lead to impaired resistance to viral infections.

V. AQUATIC TOXICITY

A. Acute Toxicity

Seven static and seven flow-through bioassays from 48 to 96-hours in duration provide a range of LC_{50} values for freshwater fish of 290 to 150,000 µg/l. Hughes and Davis (1967) demonstrated the most sensitive species as being bluegill fingerlings, Lepomis macrochirus, while Sorenson (1976) reports that the most resistant species was the green sunfish, Lepomis cyanellus. Both species were tested in static tests. Sanders and Cope (1966) provided the data for freshwater invertebrates in static bioassays. The cladoceran, Simocephalus serrulatus, was the most sensitive with an 48-hour LC_{50} value of 812 µg/l, while the stonefly, Ptaronarcys californica, was the most resistant species with an

LC_{50} value of 22,040 µg/l. In marine organisms, the chum salmon, Onchorhynchus keta, had a 48-hour flow-through LC_{50} value of 8,331 µg/l (Alderdice and Brett, 1957). Two marine invertebrates were tested in 96 or 48-hour static-renewal or static assays and produced the following LC_{50} values: bay scallop, Argopecten irradiana, with 3,490 µg/l; and the embryos of the American oyster, Crassostrea virginica, with a value of 4,330 µg/l.

B. Chronic Toxicity

One chronic life cycle freshwater test has provided a chronic value of 853 µg/l for arsenic to Daphnia magna. Pertinent data could not be located in the available literature for the chronic toxicity of arsenic to marine organisms.

C. Plant Effects

The lowest effective concentration recorded was 100 percent kill levels of 2,320 µg/l for four species of freshwater algae.

D. Residues

Bioconcentration factors for five freshwater invertebrate species and two fish species ranged from less than 1 to 17 (U.S. EPA, 1979).

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

Criteria for organic and inorganic arsenicals have been derived. However, due to public comment questioning the relevancy and accuracy of the studies used in the development of these criteria, further review is necessary before final recommendation.

The OSHA time-weighted average exposure criterion for arsenic is 10 $\mu g/m^3$.

B. Aquatic

For arsenic, the draft criterion for freshwater organisms is 57 µg/l, not to exceed 130 µg/l. For marine organisms, the draft criterion is 29 µg/l, not to exceed 67 µg/l (U.S. EPA,1979).

ARSENIC

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No. 12

Asbestos

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated asbestos and has found sufficient evidence to indicate that this compound is carcinogenic.

ASBESTOS

Summary

Numerous studies indicate that asbestos fibers introduced into the pleura, peritoneum, and trachea of rodents have induced malignant tumors. The strongest evidence for the carcinogenicity of ingested asbestos is provided by epidemiology of human populations occupationally exposed to high concentrations of airborne asbestos dust. Inhalation exposure to asbestos dust is accompanied by ingestion because a high percentage of the inhaled fibers are removed from the lung by mucociliary action and subsequently swallowed. Peritoneal mesothelioma, often in great excess, and modest excesses of stomach esophagus, colonrectal, and kidney cancer have been linked to occupational exposure to asbestos.

Pertinent data on the acute or chronic effects of asbestos to aquatic organisms were not found in the available literature.

ASBESTOS

I. INTRODUCTION

This profile is based primarily upon the Ambient Water Quality Criteria Document for Asbestos (U.S. EPA, 1979). In addition, valuable information is available from recent reviews by the International Agency for Research on Cancer (IARC, 1977) and the National Institute for Occupational Safety and Health (NIOSH, 1977).

Asbestos is a broad term applied to numerous fibrous mineral silicates composed of silicon, oxygen, hydrogen, and metal cations such as sodium, magnesium, calcium, or iron. There are two major groups of asbestos, serpentine (chrysotile or "white asbestos") and amphibole. Although chrysotile is considered to be a distinct mineral, there are five fibrous amphiboles: actinolite, amosite ("brown asbestos"), anthophyllite, crocidolite ("blue asbestos"), and tremolite. The chemical composition of different asbestos fibers varies widely, and typical formulas are presented in Table 1. Some typical physical properties of three different mineral forms of asbestos are presented in Table 2.

TABLE 1

TYPICAL FORMULAS FOR ASBESTOS FIBERS

1.	Serpentines	chrysotile	$Mg_3Si_2O_5(OH)_4$
2.	Amphiboles	amosite	$(Mg,Fe)_7Si_8O_{22}(OH)_2$
		crocidolite	$Na/_2(Mg,Fe)_5Si_8O_{22}(OH)_2$
		anthophyllite	$(Mg,Fe)_7Si_8O_{22}(OH)_2$
		tremolite	$Ca_2Mg_5Si_8O_{22}(OH)_2$
		actinolite	$Ca_2(Mg,Fe)_5Si_8O_{22}(OH)_2$

TABLE 2.

TYPICAL PHYSICAL PROPERTIES OF CHRYSOTILE (WHITE ASBESTOS), CROCIDOLITE (BLUE ASBESTOS), AND AMOSITE

	Units	Chrysotile (white asbestos)	Crocidolite (blue asbestos)	Amosite
Approximate diameter of smallest fibers	micron	0.01	0.08	0.1
Specific gravity	-	2.55	3.37	3.45
Average tensile strength	lb./inch^2	3.5×10^5	5×10^5	1.75×10^5
Modulus of elasticity	lb./inch^2	23.5×10^6	27.0×10^6	23.5×10^6

Asbestos minerals, despite a relatively high fusion temperature, are completely decomposed at temperatures of 1,000°C. Both the dehydroxylation temperature and decomposition temperature increase with increased MgO content among the various amphibole species (Speil and Leineweber, 1969).

The solubility product constants for various chrysotile fibers range from 1.0×10^{-11} to 3×10^{-12}. Most materials have a negative surface charge in aqueous systems. However, since chrysotile has a positive (+) charge, it will attract, or be attracted to, most dispersed materials. The highly reactive surface of asbestos causes many surface reactions which are intermediate between simple absorption and a true chemical reaction. The absorption of various materials on the surface of chrysotile supports the premise that the polar surface of chrysotile has a greater affinity for polar molecules (e.g., H_2O, NH_3) than for non-polar molecules (Speil and Leineweber, 1969).

Of all the asbestos minerals, chrysotile is the most susceptible to acid attack. It is almost completely destroyed within one hour in 1 N HCL at 95°C. Amphibole fibers are much more resistant to mineral acids (Lindell, 1972).

The resistance of the asbestos fibers to attack by reagents other than acid is excellent up to temperatures of approximately 100°C with rapid deterioration observed at higher temperatures. Chrysotile is completely decomposed in concentrated KOH at 200°C. In general, organic acids have a tendency to react slowly with chrysotile (Speil and Leineweber, 1969).

Chrysotile is the major type of asbestos used in the manufacture of asbestos products. These products include asbestos cement pipe, flooring products, paper products (e.g., padding), friction materials (e.g., brake linings and clutch facings), roofing products, and coating and patching compounds. In 1975, the total consumption of asbestos in the U.S. was 550,900 thousand metric tons (U.S. EPA, 1979).

Of the 243,527 metric tons of asbestos discharged to the environment, 98.3 percent was discharged to land, 1.5 percent to air, and 0.2 percent to water (U.S. EPA, 1979). Solid waste disposal by consumers was the single largest contribution to total discharges. Although no process water is used in dry mining of asbestos ore, there is the potential for runoff from asbestos waste tailings, wet mining, and iron ore mining. Mining operations can also contribute substantially to asbestos concentrations in water by air and solid waste contamination. In addition to mining and industrial discharges of asbestos, asbestos fibers, which are believed to be the result of rock outcroppings, are found in rivers and streams.

II. EXPOSURE

A. Water

Asbestos is commonly found in domestic water supplies. Of 775 recent samples analyzed by electron microscopy under the auspices of the U.S. EPA, 50 percent showed detectable levels of asbestos, usually of the chrysotile variety (Millette, 1979). Nicholson and Pundsack (1973) measured average asbestos levels of 0.3 - 1.5 µg/l in drinking water from two Eastern United States river systems. Levels of 2.0 to 172.7 x 10^6 fibers/l have been reported in Canadian tap water, the highest levels being found in unfiltered tap water near a mining area (Cunningham and Pontefract, 1971). In other studies of Canadian drinking water levels of 0.1 to 4 x 10^6 fibers/l have been reported (Kay, 1973). The U.S. EPA (1979) has concluded that about 95 percent of water consumers in the United States are exposed to asbestos fiber concentrations of less than 10^6 fibers/l. The mass concentrations of chrysotile asbestos in the water of cities with less than 10^6 fibers/l are likely to be less than 0.01 µg/l, corresponding to an adult daily intake of less than 0.02 ug. Pertinent data on the ability of aquatic organisms to bioconcentrate asbestos from water were not located in the available literature.

B. Food

There are scant data on the contribution of food products to population asbestos exposure. However, asbestos fibers and talc, which sometimes contains asbestos as an impurity, may be used in the manufacture of certain processed foods such as sugar, coated rice, vegetable oil and lard (IARC, 1977). Cunningham and Pontefract (1971) reported that certain beers and wines could contain asbestos fibers at levels similar to those found in drinking water systems (10^6 to 10^7 fibers/l).

C. Inhalation

Asbestos is present in virtually all metropolitan areas. Concentrations of asbestos in urban atmosphere are usually less than 10 ng/m^3, but may reach 100 ng/m^3 (Nicholson, et al. 1971; Nicholson and Pundesack, 1973; Sebastien, et al. 1976; IARC, 1977). Construction sites and buildings fireproofed with loose asbestos material showed the most significant contamination with individual measurements as high as 800 ng/m^3 (Nicholson, et al. 1975).

III. PHARMACOKINETICS

There are contradictory data concerning whether ingested asbestos fibers are capable of passage across the gastrointestinal mucosa (Gross, et al. 1974; Cooper and Cooper, 1978; Cunningham and Pontefract, 1973; Cunningham, et al. 1977). Most ingested asbestos particles are excreted in the feces (Cunningham, et al. 1976). However, at least one recent study (Cook and Olson, 1979) indicates that ingestion of drinking water containing amphibole fibers may result in the appearance of these fibers in the urine, thus providing evidence for passage of asbestos across the human gastrointestinal tract.

Ingestion of asbestos fibers is accompanied by swallowing of many fibers cleared from the respiratory tract by mucociliary action. More than half the asbestos inhaled will likely be swallowed (U.S. EPA, 1979). The deposition of asbestos fibers in the lung is a function of their diameter rather than length, as about 50 percent of particles with a mass median diameter of less than 0.1 um will be deposited on nonciliated pulmonary surfaces. Deposition on nasal and pharyngeal surfaces becomes important as mass median diameter approaches 1 μm and rises rapidly to become the dominant deposition site for airborne particles 10 um in diameter or greater

(Brain and Volberg, 1974). Portions of inhaled asbestos fibers which are not cleared by microciliary action may remain trapped in the lung for decades (Pooley, 1973; Langer, 1973). However, the chrysotile content of the lung does not build up as significantly as that of the amphiboles for similar exposure circumstances (Wagner, et al. 1974).

IV. EFFECTS

A. Carcinogenicity

All commercial forms of asbestos have demonstrated carcinogenic activity in mice, rats, hamsters, and rabbits. Intraperitoneal injection of various asbestos fibers has produced mesotheliomas in rats and mice (Maltoni and Annoscia, 1974; Pott and Friedrichs, 1972; Pott, et al. 1976). In rats, chronic inhalation of various types of asbestos have produced lung carcinomas and mesotheliomas (Reeves, et al. 1971, 1974; Gross, et al. 1967; Wagner, et al. 1974; Davis, et al. 1978). Intrapleural injection of asbestos fibers has produced mesotheliomas in rats, hamsters, and rabbits (Donna, 1970; Reeves, et al. 1971; Stanton and Wrench, 1972; Stanton, 1973; Wagner, et al. 1973, 1977; Smith and Hubert, 1974). The oral administration of asbestos filter material reportedly caused malignancies in rats (Gibel, et al. 1976) although other feeding studies have produced equivocal results.

Occupational exposure to chrysotile, amosite, anthophyllite, and mixed fibers containing crocidolite has resulted in high incidences of human lung cancers (Selikoff, et al. 1979; Seidman, et al. 1979; Enterline and Henderson, 1973; Henderson and Enterline, 1979; IARC, 1977). Occupational exposure to crocidolite, amosite, and chrysotile have also been associated with a large incidence of pleural and peritoneal mesotheliomas. An excess of gastrointestinal cancers has been associated in some studies with exposure to amosite, chrysotile, or mixed fibers containing crocidolite (Seli

koff, 1976; Selikoff, et al. 1979; Elmes and Simpson, 1971; Henderson and Enterline, 1979; Nicholson, et al. 1979; Seidman, et al. 1979; Newhouse and Berry, 1979; McDonald and Liddell, 1979; Kogan, et al. 1972).

In the general environment, mesotheliomas have occurred in persons living near asbestos factories and crocidolite mines and in the household contacts of asbestos workers (Wagner, et al. 1960; Newhouse and Thomson, 1965). In addition, several studies have implicated asbestos in drinking water with the development of cancer of the lung and digestive tract cancers (Mason, et al. 1974; Levy, et al. 1976; Cooper, et al. 1978, 1979). There is convincing evidence to support the contention that asbestos exposure and cigarette smoking act synergistically to produce dramatic increases in lung cancer over that from exposure to either agent alone (Selikoff, et al. 1968; Berry, et al. 1972).

In a study by Hammond, et al. (1979) involving 17,800 insulation workers, the death rate for non-smokers was 5.17 times that of a non-smoking control population. The death rate was 53.24 times that of the non-smoking control population or 4.90 times the death rate for a comparable group of non-exposed smokers. Cancers of the larynx, pharynx and buccal cavity in insulators were also found to be associated with cigarette smoking, together with some non-malignant asbestos effects such as fibrosis and deaths due to asbestosis.

B. Mutagenicity

In cultured Chinese hamster cells, chrysotile and crocidolite have produced genetic damage and morphologic transformation (Sincock and Seabright, 1975; Sincock, 1977). On the other hand, chrysotile, amosite, and anthophyllite showed no mutagenic activity toward tester strains of E. coli or S. typhimurium (Chamberlain and Tarmy, 1977).

C. Teratogenicity

Pertinent data on the possible teratogenic effects of asbestos were not located in the available literature, although transplacental passage of asbestos fibers has been reported (Cunningham and Pontefract, 1971, 1973).

D. Other Reproductive Effects

It is not known whether asbestos exposure may impair fertility or interfere with reproductive success (U.S. EPA, 1979).

E. Chronic Toxicity

The chronic ingestion of chrysotile by rats (0.5 mg or 50 mg daily for 14 months) produced no effects on the esophagus, stomach, or cecum tissue, but histological changes were seen in the ileum, particularly of the villi (Jacobs, et al. 1978).

The long-term disease entity, asbestosis, results from the inhalation of asbestos fibers and is a chronic, progressive pneumoconiosis. It is characterized by fibrosis of the lung parenchyma and produces shortness of breath as the primary symptom. Asbestos has accounted for numerous cases of occupational disablement during life as well as a considerable number of deaths among worker groups. In groups exposed at lower concentrations such as the families of workers, there is less incapacitation and although asbestosis can occur, deaths have not been reported (Anderson, et al. 1976).

Extrapulmonary chronic effects reported include "asbestos corns" from the penetration of asbestos fibers into the skin. No chronic nonmalignant gastrointestinal effects have been reported.

V. AQUATIC TOXICITY

Pertinent data concerning the effects of asbestos to either freshwater or marine organisms were not located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

The current Occupational Safety and Health Administration (OSHA) standard for an 8-hour time-weighted average (TWA) occupational exposure to asbestos is 2 fibers longer than 5 microns in length per milliliter of air (2f/ml or 2,000,000 f/m^3). Peak exposures of up to 10 f/ml are permitted for no more than 10 minutes (Fed. Reg., 1972). This standard has been in effect since July 1, 1976, when it replaced an earlier one of 5 f/ml (TWA). Great Britain also has a value of 2 f/ml as the accepted level, below which no controls are required (BOHS, 1968). The British standard, in fact, served as a guide for the OSHA standard (NIOSH, 1972).

The British standard was developed specifically to prevent asbestosis among working populations; data were felt to be lacking that would allow for determination of a standard for cancer (BOHS, 1968). Unfortunately, among occupational groups, cancer is the primary cause of excess death for workers (see "Carcinogenicity" section) with three-fourths or more of asbestos-related deaths caused from malignancy. This fact has led OSHA to propose a lower TWA standard of 0.5 f/ml (500,000 f/m^3) (Fed. Reg., 1975). The National Institute for Occupational Safety and Health (NIOSH), in their criteria document for the hearings on a new standard, have proposed a value of 0.1 f/ml (NIOSH, 1977). In the discussion of the NIOSH proposal, it was stated that the value was selected on the basis of the sensitivity of analytical techniques using optical microscopy and that 0.1 f/ml may not neces

sarily protect against cancer. Recognition that no information exists that would define a threshold for asbestos carcinogenesis was also contained in the preamble of the OSHA proposal. The existing standard in Great Britain has been questioned by Peto (1978), who estimates that asbestos disease may cause the death of 10 percent of workers exposed at 2 f/ml for a working lifetime.

The existing federal standard for asbestos emissions into the environment prohibits "visible emissions" (U.S. EPA, 1975). No numerical value was specified because of difficulty in monitoring ambient air asbestos concentrations in the ambient air or in stack emissions. Some local government agencies, however, may have numerical standards (e.g., New York, 27 ng/m^3).

No standards for asbestos in foods or beverages exist even though the use of filtration of such products through asbestos filters has been a common practice in past years. Asbestos filtration, however, is prohibited or limited for human drugs (U.S. FDA, 1976).

The draft recommended water quality criterion for asbestos particles (U.S. EPA, 1979) is derived from the substantial data which exists for the increased incidence of peritoneal mesothelioma and gastrointestinal tract cancer in humans exposed occupationally to asbestos. This derivation assumes that much or all of this increased disease incidence is caused by fibers ingested following clearance from the respiratory tract. Several studies allow the association of approximate airborne fiber concentrations to which individuals were exposed with observed excess peritoneal and gastrointestinal cancer. All of the inhaled asbestos is assumed to be eventually cleared from the respiratory tract and ingested.

The draft criterion calculated to keep the individual lifetime cancer risk below 10^{-5}, is 300,000 fibers of all sizes/liter. The corresponding mass concentration for chrysotile asbestos is approximately 0.05 ug/l. This criterion has not yet gone through the process of public review; therefore, there is a possibility that the criterion may be changed.

B. Aquatic

Because no data are available on the aquatic toxicity of asbestos, the U.S. EPA (1979) derived no aquatic criteria.

ASBESTOS

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No. 13

Barium

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

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BARIUM

18

SUMMARY

Water-soluble barium compounds are highly toxic to man. Fish and lower species of marine organisms have been shown to bioaccumulate barium. The concentration of barium in sea water ranges around 20 ug/L, while that of drinking water averages about 6 ug/L.

Soluble barium salts have a high acute toxicity. Small amounts of barium can accumulate in the skeleton of humans and animals. Barium salts are strong muscle stimulants: acute intoxication generally results in uncontrolled contractions followed by partial or complete paralysis. Cardiac disturbances including arrythmias can also occur. Barium dusts are irritant to nose, throat and eyes. Baritosis (pneumoconiosis) occurs following chronic inhalation of (fine) barium dusts. Barium sulfate used in barium enemas, swallows and artificial orthopedic bones can result in tissue injury following solubilization of the barium sulfate and/or soluble impurities. Potassium acts as an antagonist for barium induced cellular disturbances. The TWA for exposure to soluble barium compounds is 0.5 mg/m^3.

I. INTRODUCTION

Barium (Ba; atomic weight 137.34) is a yellowish-white metal of the alkaline earth group. It is relatively soft and ductile and may be worked readily. Barium has a melting point of 729°C and a boiling point of 1640°C; its density is 3.51 g/cm^3 (Kunesh 1978).

Barium characteristically forms divalent compounds. At room temperature, it combines readily and exothermically with oxygen and the halogens. It reacts vigorously with water to form barium hydroxide, $Ba(OH)_2$ (Kunesh 1978).

Barium occurs in nature chiefly as barite, crude $BaSO_4$, and as witherite, a form of $BaCO_3$, both of which are highly insoluble salts. Only barite is mined in this country (Kirkpatrick 1978).

A review of the production range (includes importation) statistics for barium (CAS. No. 7440-39-3) which are listed in the initial TSCA Inventory, (U.S. EPA 1979) has shown that between 100,000 and 900,000 pounds of this chemical were produced/imported in 1977*.

*This production range information does not include any production/importation data claimed as confidential by the person(s) reporting for the TSCA inventory, nor does it include any information which would compromise Confidential Business Information. The data submitted for the TSCA Inventory, including production range information, are subject to the limitations contained in the Inventory Reporting Regulations (40 CFR 710).

C. Environmental Occurrence

The flow of barium in the United States has been traced for the year 1969, during which time consumption of barium totaled 1.87 billion pounds. It was estimated that 30.8 million pounds of barium were emitted to the atmosphere. Nearly 18 percent of the emissions resulted from the processing of barite, more than 28 percent from chemical production, 26 percent from the combustion of coal, and 23 percent from the manufacture of miscellaneous end products (U.S. EPA 1972).

The concentration of barium in sea water is generally accepted as about 20 ug/L, with lower concentrations in the surface waters than at greater depths. Barium ions are generally removed from solution quite rapidly by adsorption, sedimentation and precipitation (U.S. EPA 1973). Concentrations of barium in this country's drinking water supplies generally range from less than 0.6 ug/L to about 10 ug/L, although a few midwestern and western states have had upper limits of 100 to 300 ug/L (U.S. EPA 1976).

Due to the common use of barite as a weighting agent in drilling muds, the resultant contamination of sediments near drilling sites was studied. The average content of barium in benthic sediments from the Southern California Bight was 637 parts per million (ppm), with a range from 43 to 1899 ppm. This area includes active drilling sites where barium contamination is expected. The concentration values were compared with the average 879 ppm barium found in mainland intertidal sediments and the 388 ppm determined in the channel island intertidal sediments. The lower barium content of the island sediments was attributed to the volcanic soil of the islands; however, the higher barium concentration of the mainland could not be traced to either natural or anthropogenic origin. Due to variations in soil sources it is questionable whether barium concentrations determined elsewhere could be used as reference values for this study (Chow 1978).

In two studies correlating trace metal concentrations in the environment with that in scalp hair of the inhabitants, barium was measured in the house dust collected in four communities. Geometric mean values of barium determined in house dust samples from the New York City area were as follows: 65.2 ug Ba/g dust in Riverhead, 137.6 ug/g in Queens, and 312.4 ug/g in the Bronx (USEPA, 1978b). The geometric mean value for barium measured in house dust in Ridgewood, New Jersey was 330.0 ug/g (U.S. EPA 1978c).

Barium and its compounds are used industrially as weighting agents in oil and gas well drilling muds; as coloring agents in glass, ceramics, paint, and pigments; as filler in rubber; and as antismoking agents in diesel fuel (U.S. EPA 1972; NAPCA 1969). In medicine, barium sulfate is used as an x-ray contrast medium because of its extreme insolubility and its ability to absorb x-rays (Kirkpatrick 1978; U.S. EPA 1978a).

II. EXPOSURE

A. Environmental Fate

Due to the high reactivity of barium, it is not found in its elemental state in the environment. In sea water, the naturally present sulfate and carbonate tend to precipitate any water-soluble barium components. Thus, the sediment usually has a higher concentration of barium than its corresponding water source (Guthrie 1979).

B. Bioconcentration

Due to the toxicity of soluble barium salts to man, the bioaccumulation of the element has been a concern. Barium can be concentrated in goldfish by a factor of 150. Concentration factors for barium listed in one study are 17,000 in phytoplankton, 900 in zooplankton, and 8 in fish muscle (U.S. EPA 1973). Thus, ingestion of fish by man can be a source of barium exposure.

Another study conducted on various species of marine organisms produced the following results (Guthrie 1979): Barnacles bioaccumulated about five times greater concentration of barium than was in the water, while oysters and clams contained concentrations of the element similar to that present in the water. Crabs and polychaetes were also analyzed for barium and were found to contain a significantly smaller quantity than that present in the sediment on which they dwell. However, no significant differences were noted between the concentration of barium in the two organisms and the concentrations in the water column.

In man, studies have been conducted to determine a correlation between barium in the environment, measured as house dust, and the concentration of barium found in scalp hair of the inhabitants. A significant positive correlation has been determined between the geometric mean concentrations of the element in house dust and hair. Other covariants of significant value measured in the studies were sex, hair length, and, in children less than 16 years old, age (U.S. EPA 1978b; U.S. EPA 1978c).

III. PHARMACOKINETICS

Soluble barium is retained by muscle tissue for about 30 hours, after which the amount of retained barium decreases slowly (NAPCA 1969). Small amounts of barium become irreversibly deposited in the skeleton. However, the acceptance level is limited, as quantitative analysis of human bone reveals no accumulation of barium from birth to death. Barium levels averaged 7 ug/g ashed bone. Very little barium is retained by the liver, kidneys, or spleen, and practically none by the brain, heart, or hair. Transient high concentrations are seen in the liver with lesser amounts in lung and spleen following acute experimental dosing.

Barium administered orally or intraperitoneally as $BaCl_2$ to weanling male rats at doses of 1, 5, 25, or 125 mg/kg was taken up rapidly by the soft tissues (30 mins), showed slow uptake by the skeleton (2 hrs) and was excreted primarily in the feces (Clary and Tardiff, 1974). No retention data were reported.

Pulmonary clearance rates of inhaled radioactive ^{133}Ba salts ranged from several hours for the soluble $BaCl_2$ to hundreds of days for Ba^{++} in fused clay . Large amounts of barium were excreted in the feces; a lesser amount was excreted in the urine. Although $BaSO_4$ is "insoluble" in water, 50% of $^{133}BaSO_4$ dissolved in a simulated biological fluid within 2-3 days, indicating that solubilization is relatively rapid.

IV. HEALTH EFFECTS

A. Carcinogenicity

Bronchogenic carcinoma developed in rats injected with radioactive ^{35}S (unspecified dose) labelled barium sulfate (Patty 1963). $BaSO_4$ powder (particle size undefined) injected intrapleurally in female and male mice produced a mesothelioma in only 1 out of 30 animals. No other pathological lesions were investigated or reported. Saline controls (32) resulted in no mesotheliomas. Barium sulfate had an oncogenic potency similar to that of glass powder and aluminum oxide. It therefore appears likely that the observed tumor was due to foreign-body-oncogenesis (Wagner).

B. Acute and Chronic Toxicity

The soluble salts of barium are highly toxic when ingested. Barium chloride and barium carbonate, two of the soluble compounds, have been reported to cause toxic symptoms of a severe but usually nonfatal degree. Seven grams of barium chloride (≈4.5 g Ba) taken orally produced severe abdominal pain and near-collapse, but not death (NAPCA 1969). However, Patty (1963) indicates 800 to 900 mg of barium chloride (550-600 mg Ba) to be a fatal human dose. Few cases of industrial poisoning from soluble barium salts have been reported. Most of these have been cases of accidental ingestion (NAPCA 1969).

Ingested soluble barium compounds produce a strong stimulating effect on all muscles of the body. The effect on the heart muscle is manifested by irregular contractions followed by arrest of systolic action. Gastrointestinal effects include vomiting and diarrhea. Central nervous system effects observed include violent tonic and clonic spasms followed in some cases by paralysis (NAPCA 1969).

Death resulting from barium exposure may occur in a few hours or a few days, depending on the dose and solubility of the barium compound. A death attributed to barium oxide poisoning has been reported. However, the usual effect of exposure to dusts and fumes of barium oxide, barium sulfide, and barium carbonate is irritation of eyes, nose, throat and the skin (NAPCA 1969).

Some of the $BaSO_4$ used in orthopedic bone cements has been shown to escape into surrounding tissues (Rae 1977). Mouse peritoneal macrophages exposed to barium sulfate (10 particles of unspecified size/macrophage) for periods up to 144 hours showed a marked cytoplasmic vacuolization. Following cessation of exposure only partial recovery occurred. No cell membrane damage was observed (Rae 1977). The use of barium sulfate in barium swallows and enemas resulted in severe toxic affects on rupture of the intestinal tract (Gardiner and Miller 1973, Bayer et al. 1974).

Inhalation of barium compounds is known to cause a benign respiratory affliction (pneumoconiosis) called baritosis, which has been reported in workers exposed to finely divided barium sulfate in Italy, in barite miners in the United States, Germany, and Czechoslovakia, and among workers exposed to barium oxide. Generally, baritosis produces no symptoms of emphysema or bronchitis, and lung function tests show no respiratory incapacity, although some afflicted workers complain of dyspnea upon exertion. In the majority of cases nodulation disappears if exposure to the barium compound is stopped (NAPCA 1969). Aspirated $BaSO_4$ can result in granulomas of the lung and other sites in man (Patty 1963).

Suicidal ingestion of a facial depilatory containing 15.8 g of BaS resulted in paralysis of head, neck, arms, and trunk as well as respiratory paralysis. Therapy with $MgSO_4$, saline and potassium resulted in recovery within 24 hours (Gould et al. 1973).

Acute oral toxicity values for barium carbonate were: mouse LD = 200 mg/kg; rat LD = 50-200 mg/kg, LD_{50} = 1480 $\pm$ 340 mg/kg; rabbit LD = 170-300 mg/kg. For barium chloride oral toxicity values were: mouse LD = 7-14 mg/kg; rat LD = 355-533 mg/kg; rabbit LD = 170 mg/kg; dog LD = 90 mg/kg. For barium flouride the acute oral LD for guinea pigs was 350 mg/kg (NAPCA 1969).

C. Other Relevant Information

Potassium acts as an in vitro antagonist of barium. Cardiac effects such as arrythmias exerted by barium are also reversed rapidly by potassium. Barium induces hypokalemia apparently by promoting a shift of potassium from plasma into cells. The prolongation of action-potentials and depolarization of smooth and skeletal muscle by barium are thought to be due to barium induced decreases in potassium conductance. In addition, barium can replace sodium to produce and/or prolong action potentials and can also substitute for calcium in neurosecretory processes as described below (Peach 1975).

Barium chloride has been shown to cause arterial contractions in in vitro preparations of human digital arteries at concentrations of 10^{-4} to 10^{-6} M (Jauernig and Moulds 1978). This activity was approximately 40 to 50 fold more than that of potassium chloride. At $BaCl_2$ concentrations above 10^{-2} M contractions developed very slowly. The action of $BaCl_2$ was inhibited by veraparmil, a calcium antagonist, at $BaCl_2$ contractions below 10^{-2} M.

V. AQUATIC TOXICITY

According to an EPA report, experimental data indicate that in fresh and marine waters, the soluble barium concentration would need to exceed 50 mg/L before toxicity to aquatic life would be expected (U.S. EPA 1976). Furthermore, in most natural waters, sufficient sulfate or carbonate is present to precipitate barium in the water to a virtually insoluble, non-toxic compound.

Soluble barium salts, however, are quite toxic. It has been reported that 10 to 15 mg/L of barium chloride (9.9 mg/L Ba) was lethal to an aquatic plant and two species of snails (species and origin unspecified). Bioassay with this same barium salt showed the LC_{90} for Coho Salmon to be 158 mg/L (104 mg/L Ba) (U.S. EPA 1973).

VI. GUIDELINES

A. Human Health

The OSHA Time Weighted Average for exposure to barium (soluble compound) is 0.5 mg/m^3 (29 CFR 1910:1000).

B. Aquatic

There is no established criterion for barium in the aquatic environment. The U.S. EPA (1973) suggests, however, that concentrations of barium equal to or exceeding 1.0 mg/L constitute a hazard in the marine environment, and levels less than 0.5 mg/L present minimal risk of deleterious effects.

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No. 14

Benzal Chloride

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

No. 14

Benzal Chloride

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WASHINGTON, D.C. 20460

APRIL 30, 1980

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BENZAL CHLORIDE

Summary

Benzal chloride has been reported to induce papillomas, carcinomas, and leukemia in mice. Details of this work were not available for assessment.

Mutagenic effects of benzal chloride exposure have been reported in Salmonella, Bacillus, and E. coli.

There is no available information on the teratogenic or adverse reproductive effects of the compound.

I. INTRODUCTION

Benzal chloride, CAS registry number 98-87-3, is a fuming, highly refractive, colorless liquid. It is made by free radical chlorination of toluene and has the following physical and chemical properties (Windholz, 1976; Verschueren, 1977):

Formula:	$C_7H_6Cl_2$
Molecular Weight:	161.03
Melting Point:	-16°C
Boiling Point:	207°C
Density:	1.256^{14}
Vapor Pressure:	0.3 torr @ 20°C
Solubility:	alcohol, ether insoluble in water

Benzal chloride is used almost exclusively for the manufacture of benzaldehyde. It can also be used to prepare cinnamic acid and benzoyl chloride (Sidi, 1971).

II. EXPOSURE

A. Water

Benzal chloride is converted to benzaldehyde and hydrochloric acid on contact with water (Sidi, 1971).

B. Food

Pertinent data could not be located in the available literature.

C. Inhalation

It is likely that the only source of benzal chloride in the air is production facilities. The compound will hydrolyze in moist air to give benzaldehyde and hydrochloric acid. Inhaled benzal chloride will probably produce effects similar to those of inhaled hydrogen chloride.

D. Dermal

Benzal chloride is irritating to the skin (Sidi, 1971).

III. PHARMACOKINETICS

Pertinent data on the pharmacokinetics of benzal chloride could not be located in the available literature.

IV. EFFECTS

A. Carcinogenicity

In a study of Matsushito, et al. (1975) benzal chloride, along with several other compounds, was found to induce carcinomas, leukemia, and papillomas in mice. The details of the study were not available, but benzal chloride was shown to possess a longer latency period than benzotrichloride before the onset of harmful effects.

B. Mutagenicity

Yasuo, et al. (1978) tested the mutagenicity of several compounds including benzal chloride in microbial assay systems which include the rec-assay using Bacillus subtilis, the reversion assay using E. coli, and the Ames assay using Salmonella typhimurium, with or without metabolic activation. Benzal chloride was positive in the rec-assay without activation and in the reversion assays using S. typhimurium and E. coli with metabolic activation.

C. Teratogenicity, Other Reproductive Effects and Chronic Toxicity

Pertinent data could not be located in the available literature.

D. Acute Toxicity

The oral LD_{50}'s for mice and rats exposed to benzal chloride are 2,462 mg/kg and 3,249 mg/kg, respectively (NIOSH, 1978).

V. AQUATIC TOXICITY

Pertinent aquatic toxicity data could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

There are no existing guidelines or standards for exposure to benzal chloride.

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No. 15

Benzene

Health and Environmental Effects

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APRIL 30, 1980

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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated benzene and has found sufficient evidence to indicate that this compound is carcinogenic.

BENZENE

Summary

Benzene is a widely used chemical. Chronic exposure to it causes hematological abnormalities. Benzene is not mutagenic to bacteria, but recent evidence shows it to be carcinogenic in animals. Also, benzene has been shown to be leukemogenic in humans. There is suggestive evidence that benzene may be teratogenic and may cause reduced fertility.

Benzene has been shown to be acutely toxic to aquatic organisms over a concentration range of 5,800 to 495,000 µg/l. The marine fish striped bass was the most sensitive species tested.

BENZENE

I. INTRODUCTION

This profile is based on the draft Ambient Water Quality Criteria Document for Benzene (U.S. EPA, 1979).

Benzene (Benzol C_6H_6; molecular weight 78.1) is a volatile, colorless, liquid hydrocarbon produced principally from coal tar distillation, from petroleum by catalytic reforming of light napnthas, and in coal processing and coal coking operations (Weast, 1972; Ayers and Muder, 1964; U.S. EPA, 1976a). Benzene has a boiling point of 80.1°C, a melting point of 5.5°C, a water solubility of 1,780 mg/l at 25°C, and a density of 0.87865 g/ml at 20°C. The broad utility spectrum of benzene includes its use as: an intermediate for synthesis in the chemical and pharmaceutical industries, a thinner for lacquer, a degreasing and cleaning agent, a solvent in the rubber industry, an antiknock fuel additive, a general solvent in laboratories and in the preparation and use of inks in the graphic arts industries.

Current production of benzene in the U.S. is over 4 million metric tons annually, and its use is expected to increase when additional production facilities become available (Fick, 1976).

II. EXPOSURE

A. Water

A report by the National Cancer Institute (1977) noted benzene levels of 0.1 to 0.3 ppb in four U.S. city drinking water supplies. One measurement from a groundwater well in Jacksonville, Florida showed levels higher than 100 ppb. One possible source of benzene in the aquatic environment is from cyclings between the atmosphere and water (U.S. EPA, 1976b). Concentrations of benzene upstream and downstream from five benzene

production or consumption plants ranged from less than 1.0 to 13.0 ppb, with an average of 4.0 ppb (U.S. EPA, 1977a).

B. Food

Benzene has been detected in various food categories: fruits, nuts, vegetables, dairy products, meat, fish, poultry, eggs, and several beverages (Natl. Cancer Inst., 1977). NCI estimated that an individual might ingest as much as 250 µg/day from these foods. The U.S. EPA (1979) has estimated the weighted average bioconcentration factor of benzene for the edible portion of fish and shellfish consumed by Americans to be 6.9. This estimate is based on the octanol/water partition coefficient of benzene.

C. Inhalation

The respiratory route is the major source of human exposure to benzene, and much of this exposure is by way of gasoline vapors and automotive emissions. American gasolines contain an average of 0.8 percent benzene (by weight) (Goldstein, 1977a), and automotive exhausts contain an average of 4 percent benzene (by weight) (Howard and Durkin, 1974). Concentrations of benzene in the ambient air of gas stations have been found to be 0.3 to 2.4 ppm (Natl. Acad. Sci/Natl. Res. Council, 1977). Lonneman and coworkers (1968) measured an average concentration of 0.015 ppm in Los Angeles air with a maximum of 0.057 ppm. The rural background level for benzene has been reported as 0.017 ppb (Cleland and Kingsbury, 1977).

III. PHARMACOKINETICS

A. Absorption

The respiratory absorption of benzene by humans has been measured several times and found to be 40 to 50 percent retained on exposures to 110 ppm or less (Srbova, et al. 1950; Teisinger, at al. 1952; Hunter and Blair, 1972; Nomiyama and Nomiyama, 1974). Absorption was slightly less efficient,

28 to 34 percent, on exposure to 6,000 ppm (Duvoir, et al. 1946). Deichmann, et al. (1963) demonstrated that rats exposed to benzene (44 to 47 ppm) for long periods of time maintained blood benzene levels of approximately 4.25 mg/l.

B. Distribution

Free benzene accumulates in lipid tissue such as fat and bone marrow, and benzene metabolites accumulate in liver tissue and bone marrow (U.S. EPA, 1977b).

C. Metabolism

Benzene is metabolized by the mixed-function oxidase system to produce the highly reactive arene oxide (Rusch, et al. 1977). Arene oxide can spontaneously rearrange to form phenol, undergo enzymatic hydration followed by dehydrogenation to form catechol or a glutathione derivative, or bind covalently with cellular macromolecules. Evidence has accumulated that a metabolite of benzene is responsible for benzene toxicity, in light of the fact that a protection from benzene toxicity is afforded by inhibitors of benzene metabolism (Nomiyama, 1964; Andrews, et al. 1977). The specific metabolite that produces benzene toxicity has not yet been identified, but likely candidates are benzene oxide, catechol, and hydroquinone, or the corresponding semiquinones (U.S. EPA, 1977b).

D. Excretion

Phenol measurement (free plus combined) of the urine of human volunteers indicated that 50 to 87 percent of the retained benzene was excreted as phenol (Hunter and Blair, 1972). The highest concentration of phenol was found in the urine within about 3 hours from termination of exposure. Elimination via the lungs was no more than 12 percent of the retained dose.

IV. EFFECTS

A. Carcinogenicity

On subcutaneous, dermal, oral, and inhalation exposure of rats and mice to benzene, animal experiments have failed to support the view that benzene is leukemogenic (U.S. EPA, 1979). Recent evidence suggests, however, that benzene is an animal carcinogen (Maltoni and Scarnato, 1979). The evidence that benzene is a leukemogen for man is convincing and has recently been reviewed by the Natl. Acad. Sci./Natl. Res. Coun. (1976), Natl. Inst. Occup. Safety and Health (1977), and U.S. EPA (1977b). Vigliani and Saita (1964) calculated a 20-fold higher risk of acute leukemia in workers in northern Italy exposed to benzene. In some studies of acute leukemia where benzene exposure levels have been reported, the concentrations have generally been above 100 ppm (Aksoy, et al. 1972, 1974a,b, 1976a,b; Vigliani and Fourni, 1976; Vigliani and Saita, 1964; Kinoshita, et al. 1965; Sellyei and Kelemen, 1971). However, other studies have shown an association of leukemic evidence to benzene levels less than 100 ppm (Infante et al., 1977; Ott et al., 1978).

B. Mutagenicity

Benzene has not shown mutagenic activity in the Salmonella/microsome in vitro bioassay (Lyon, 1975; Shahin, 1977; Simmon, et al. 1977).

C. Teratogenicity

With rats exposed to 100 to 2,200 ppm benzene during days 6 to 15 of gestation some skeletal deformities were observed in their offspring (Amer. Pet. Inst., 1978). Pregnant mice given single subcutaneous injections of benzene (3 ml/kg) on days 11 to 15 of gestation produced fetuses

with cleft palates, agnathia, and microagnathia, when delivered by caesarean section on day 19 (Watanabe and Yashida, 1970).

D. Other Reproductive Effects

Gofmekler (1968) found complete absence of pregnancy in female rats exposed continuously to 209.7 ppm benzene for 10 to 15 days prior to impregnation. One of ten rats exposed to 19.8 ppm exhibited resorption of embryos. The number of offspring per female exhibited an inverse relationship to benzene exposure levels from 0.3 to 209.7 ppm.

E. Chronic Toxicity

In humans, pancytopenia (reduction of blood erythrocytes, leukocytes, and platelets) has clearly been related to chronic benzene exposure (Browning, 1965; Goldstein, 1977b; Intl. Labour Off., 1968; Snyder and Kocsis, 1975). Also, impairment of the immunological system has been reported with chronic benzene exposure (Lange, et al. 1973a; Smolik, et al. 1973). Wolf, et al. (1956) reported that the no-effect level for blood changes in rats, guinea pigs, and rabbits was below 88 ppm in the air when the animals were exposed for 7 hours per day for up to 269 days.

F. Other Relevant Information

In rabbits and rats injected subcutaneously with 0.2 mg/kg/day benzene, the frequency of bone marrow mitosis with chromosomal aberrations increased from 5.9 percent to 57.8 percent after an average of 18 weeks (Kissling and Speck, 1971; Dobrokhotov, 1972). In patients with benzene induced aplastic anemia, lymphocyte chromosome damage, i.e., abnormal karyo-type and deletion of chromosomal material, has been found (Pollini and Colombi, 1964).

V. AQUATIC TOXICITY

A. Acute

Acute toxicity values for freshwater fish are represented by 96-hour static LC_{50} values of 20,000 to 22,490 µg/l for the bluegill, Lepomis macrochirus, to 386,000 µg/l for the mosquitofish, Gambusia affinis, with goldfish, Carassius auratus, fathead minnows, Pimephales promelas, and guppies, Poecilia reticulatius, being somewhat more resistant than the bluegill (U.S. EPA, 1979). Only one study was available for the acute effects of benzene to freshwater invertebrates. A 48-hour static LC_{50} value of 203,000 µg/l was obtained for the cladoceran Daphnia magna. LC_{50} values for marine fish were reported as 5,800 and 10,900 µg/l for striped bass, Morone saxatilis, and 20,000 to 25,000 µg/l for Pacific herring, Clupea pallasi, and anchovy, Engraulis mordax, larvae. Marine invertebrates were much more resistant with LC_{50} values of 27,000, 108,000, and 450,000 µg/l reported for grass shrimp, Palaemonetes pugio, dungeness crab, Cancer magister, and the copepod, Tigricopus californicus, respectively (U.S. EPA, 1979).

B. Chronic Toxicity

The only chronic toxicity test conducted on an aquatic species was performed on the freshwater cladoceran, Daphnia magna. There were no observed effects to these organisms at concentrations as high as 98,000 µg/l. Pertinent information of the chronic effects of benzene on marine fish and invertebrates could not be located in the available literature.

C. Plant Effects

A concentration of 525,000 µg/l was responsible for a 50 percent reduction in cell numbers at 48-hours for the freshwater algae, Chlorella vulgaris, while marine plants were reported as having growth inhibition at

concentrations ranging from 20,000 to 100,000 µg/l for the diatom, Skeletonema costatum, with the dinoflagellate, Amphidinium carterae, and the algae, Cricosphaera carterae, being intermediate in sensitivity with effective concentrations of 50,000 µg/l.

D. Residues

A bioconcentration factor of 24 was obtained for organisms with a lipid content of 8 percent.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor aquatic criteria derived by U.S. EPA (1979) which are summarized below have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

Existing air standards for occupational exposure to benzene include 10 ppm, an emergency temporary level of 1 ppm by the U.S. Occupational Safety and Health Administration (Natl. Inst. Occup. Safety Health, 1974, 1977), and 25 ppm by the American Conference of Governmental Industrial Hygienists (ACGIH, 1971). Based on human epidemiology data, and using a modified "one-hit" model, the EPA (1979) has estimated levels of benzene in ambient water which will result in specified risk levels of human cancer:

Exposure Assumotions (per day)	Risk Levels and Corresponding Draft Criteria			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish.	0	0.15 µg/l	1.5 µg/l	15 µg/l
Consumption of fish and shellfish only.	0	2.5 µg/l	25 µg/l	250 µg/l

8. Aquatic

Criterion for the protection of freshwater organisms have been drafted at 3,100 µg/l as a 24-hour average concentration not to exceed 7,000 µg/l. For marine organisms criterion have been drafted as a 24-hour average concentration of 920 µg/l not to exceed 2,100 µg/l.

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No. 16

Benzidine

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated benzidine and has found sufficient evidence to indicate that this compound is carcinogenic.

BENZIDINE

Summary

Benzidine is a known carcinogen and has been linked to an increased incidence of bladder cancer in humans and to cancers and tumors in experimental animals. Benzidine is mutagenic in the Ames assay and gives positive results in a test measuring DNA synthesis inhibition in HeLa cells.

Pertinent data could not be located in the available literature concerning the toxic effects of benzidine to aquatic organisms.

BENZIDINE

I. INTRODUCTION

Benzidine (4,4'-diaminobiphenyl) is an aromatic amine with a molecular weight of 184.24. It exists at environmental temperature as a grayish-yellow, white, or reddish-gray crystalline powder. Its melting point is 128°C, and its boiling point is 400°C. Benzidine's amino groups have pKa values of 4.66 and 3.57 (Weast, 1972). Two and one-half liters of cold water will dissolve 1 g of benzidine, and its solubility increases as water temperatures rise. Dissolution into organic solvents greatly increases solubility. Benzidine is easily converted to and from its salt. Diazotization reactions involving benzidine will result in colored compounds which are used as dyes in industry (U.S. EPA, 1979).

II. EXPOSURE

A. Water

Residential water supplies could be contaminated with benzidine and its derivatives if the industrial effluent containing these chemicals were discharged into water supplies, however, to date U.S. EPA (1979) finds no reports of such contamination.

B. Food

While food may become contaminated with benzidine due to poor industrial hygiene, U.S. EPA (1979) reports that the ingestion of contaminated food is not a real contribution to benzidine toxicity.

The U.S. EPA (1979) has estimated a weighted average bioconcentration factor (BCF) of 50 for benzidine, on octanol/water partition coefficients and other factors.

C. Inhalation

Due to poor industrial hygiene and the use of open systems in the early days of the chemical and dye industries, inhalation was formerly a principal route of entry for benzidine and its derivatives into the body. At present workers wear respirators and protective clothing to avoid exposure when cleaning equipment (Haley, 1975).

D. Dermal

Skin absorption is the most important route for entry of benzidine into the body. Intact skin is easily penetrated by the powdery benzidine base and is penetrated less readily by 3,3'-dimethoxybenzidine and 3,3'-dichlorobenzidine. High environmental air temperatures and humidity increase skin absorption of benzidine, 3,3'-dimethoxybenzidine, 3,3'-dichlorobenzidine, and 3,3'-dimethylbenzidine (U.S. EPA, 1979).

III. PHARMACOKINETICS

A. Absorption and Distribution

Benzidine is rapidly absorbed into the bodies of intraveneously injected rats, with maximum concentrations of free and bound benzidine occurring at two and three hours, respectively. The highest concentration of benzidine was found in the blood followed by the liver, kidney, spleen, heart, and lung (Soloimskaya, 1968). Four hours after rats received intraperitoneal injections of 100 mg benzidine/kg, high concentrations of the compound were found in the stomach, stomach contents, and small intestine;

12 hours after administration, benzidine was found in the small intestine and its contents. Benzidine levels in the liver, the target organ for toxicity in the rat, remained relatively high and constant throughout the 12-hour period. The conjugated material, indicative of the presence of metabolites, was high in urine and tissues at 12 hours (Baker and Deighton, 1953). In rats given 20 mg of 3,3'-dimethylbenzidine subcutaneously once a week for eight weeks, amines were concentrated in the Zymbal's gland, followed by the kidney, omentum, spleen, and liver (Pliss and Zabezhinsky, 1970).

B. Metabolism and Excretion

The urine of humans exposed to benzidine contained a number of metabolites: N-hydroxyacetylamino benzidine, 3-hydroxybenzidine, 4-amino-4-oxybiphenyl, and mono- and diacetylbenzidine (Engelbertz and Babel, 1953; Troll, et al. 1963; Sciarini and Meigs, 1961; Vigliani and Barsotti, 1962). Benzidine metabolites in other species generally differ considerably from those in humans, although 3-hydroxybenzidine and its conjugation products are common to both animals and humans (Haley, 1975).

The half-life of benzidine in blood was 68 hours for the rat and 88 hours for the dog. Rats, dogs, and monkeys excreted 97, 96, and 83 percent, respectively, within one week of an 0.2 mg/kg dose of benzidine. The respective excretion rates for 3,3'-dichlorobenzidine were 98, 97, 88.5 percent. Dogs and monkeys excreted free benzidine in the urine and dichlorobenzidine in the bile while rats excreted both compounds via the bile (Kellner, et al. 1973).

Workers exposed to benzidine, who perspire freely and have wet skin, contain a higher concentration of benzidine in the urine (U.S. EPA, 1979).

IV. EFFECTS

A. Carcinogenicity

Benzidine is a proven human carcinogen. Its primary site of tumor induction is the urinary bladder (U.S. EPA, 1979).

Workers exposed to benzidine have a carcinogenicity risk 14 times higher than that of the unexposed population (Case, et al. 1954). The incidence of bladder tumors in humans resulting from occupational exposures to aromatic amines (benzidine) was first researched in Germany in 1895. In the United States, the first cases of this condition were diagnosed in 1931 and reported in 1934.

A number of studies document the high incidence of bladder tumors in workers exposed to benzidine and other aromatic amines (Gehrman, 1936; Case, et al. 1954; Scott, 1952; Deichmann and Gerarde, 1969; Hamblin, 1963; Rye, et al. 1970; Int. Agency Res. Cancer, 1972; Riches, 1972; Sax, 1975; Zavon, et al. 1973; Mancuso and El-Attar, 1966, 1967; Kuzelova, et al. 1969; Billiard-Duchesne, 1960; Vigliani and Barsotti, 1962; Forni, et al. 1972; Tsuchiya, et al. 1975; Goldwater, et al. 1965). Initial exposure concentration, exposure duration, and years of survival following exposure as well as work habits and personal hygiene are involved in the development of carcinomas where benzidine appears to be implicated (Rye, et al. 1970).

Benzidine has also produced carcinogenic effects or tumors in the mouse (hepatoma, lymphoma), the rat (hepatoma,

carcinoma of the Zymbal's gland, adenocarcinoma, sarcoma, mammary gland carcinoma), the hamster (hepatoma, liver carcinoma, cholangioma), the rabbit (bladder tumor, gall bladder tumor) and the dog (bladder tumor) (Haley, 1975).

At present, there is no evidence indicating that 3,3'-dimethylbenzidine, 3,3'-dimethoxybenzidine, or 3,3'-dichlorobenzidine are human bladder carcinogens (Rye, et al. 1970).

B. Mutagenicity

In the Ames test, benzidine is mutagenic to Salmonella typhimurium strains TA1537, TA1538, and TA98. Benzidine produces positive results in a DNA synthesis inhibition test using HeLa cells (Ames, et al. 1973; McCann, et al. 1975; Garner, et al. 1975; U.S. EPA, 1978; U.S. EPA, 1979).

C. Teratogenicity

No teratogenic effects of benzidine have been reported in humans. Mammary gland tumors and lung adenomas occurred in progeny of female mice that received 8 to 10 mg of 3,3'-dimethylbenzidine in the last week of pregnancy. The tumors may have resulted from transplacental transmission of the chemical or from its transfer to neonates in milk from dosed mothers (Golub, et al. 1974).

D. Other Reprodutive Effects

Pertinent data could not be located in the available literature.

E. Chronic Toxicity

Glomerulonephritis and nephrotic syndrome were produced in Sprague-Dawley rats fed 0.043 percent N,N'-diacetylbenzidine, a metabolite of benzidine, for at least two months (Harman, et al. 1952; Harman, 1971). Glomerulonephritis also developed in rats fed

benzidine (Christopher and Jairam, 1970), and in rats receiving injections either 100 mg subcutaneously or 100 or 200 mg intraperitoneally of N,N'-diacetylbenzidine. The severity of the lesions in the later study was dose-related (Bremner and Tange, 1966).

Mice fed 0.01 and 0.08 percent benzidine dihydrochloride exhibited decreased carcass, liver, and kidney weights, increased spleen and thymus weights, cloudy swelling of the liver, vacuolar degeneration of the renal tubules, and hyperplasia of the myeloid elements in the bone marrow and of the lymphoid cells in the spleen and thymic cortex. There was a dose dependent weight loss of 20 percent in males and 7 percent in females (Rao, et al. 1971).

F. Other Relevant Information

Dermatitis, involving both benzidine and its dimethyl derivative, has been reported in workers in the benzidine dyestuff industry. Individual sensitivity played a large role in the development of this condition (Schwartz, et al. 1947).

V. AQUATIC TOXICITY

Pertinent data could not be located in the available literature concerning the toxic effects of benzidine to aquatic organisms.

VI. EXISTING GUIDELINES AND STANDARDS

Both the human health and aquatic criteria derived by U.S. EPA (1979), which are summarized below, have not yet gone through the process of public review; therefore, there is a possibility that these criteria may be changed.

A. Human

The ambient water concentration standard for benzidine is zero, due to potential carcinogenic effects of exposure to

benzidine by ingestion of water and contaminated aquatic organisms. U.S. EPA may set standards at an interim target risk level in the range of 10^{-5}, 10^{-6}, or 10^{-7} with respective corresponding criteria of 1.67×10^{-3} µg/l, 1.67×10^{-4}, and 1.67×10^{-5} µg/l.

B. Aquatic

Criteria for the protection of freshwater or marine aquatic organisms were not drafted, due to a lack of toxicological evidence (U.S. EPA, 1979).

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No. 17

Benz(a)anthracene

Health and Environmental Effects

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APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated benz(a)anthracene and has found sufficient evidence to indicate that this compound is carcinogenic.

BENZ(a)ANTHRACENE

SUMMARY

Benz(a)anthracene is a member of the polycyclic aromatic hydrocarbons (PAH) class. Although the PAH class contains several well-known potent carcinogens, benz(a)anthracene displays only weak carcinogenic activity. Benz(a)-anthracene apparently does not display remarkable acute or chronic toxicity other than the capability to induce tumors on the skin of mice. Although exposure to benz(a)-anthracene in the environment occurs in conjunction with exposure to other PAH, it is not known how these compounds may interact in human systems. Furthermore, the specific effects of benz(a)anthracene in humans are not known.

The only toxicity data for any of the polycyclic aromatic hydrocarbons is an 87 percent mortality of freshwater fish exposed to 1,000 µg/l benz(a)anthracene for six months.

I. INTRODUCTION

This profile is based primarily on the Ambient Water Quality Criteria Document for Polynuclear Aromatic Hydrocarbons (U.S. EPA, 1979a) and the Multimedia Health Assessment Document for Polycyclic Organic Matter (U.S. EPA, 1979b).

Benz(a)anthracene ($C_{18}H_{12}$) is one of the family of polycyclic aromatic hydrocarbons (PAH) formed as a result of incomplete combustion of organic material. Benz(a)anthracene has the following physical/chemical properties (U.S. EPA, 1979b):

Melting point:	159.5-160.5°C
Boiling Point:	400°C
Vapor Pressue:	1.10×10^{-7} torr

PAH, including benz(a)anthracene, are ubiquitous in the environment, being found in ambient air, food, water, soils, and sediment (U.S. EPA, 1979b). The PAH class contains a number of potent carcinogens (e.g., benzo(a)pyrene), weak carcinogens (e.g., benz(a)anthracene), and cocarcinogens (e.g., fluoranthene), as well as numerous non-carcinogens (U.S. EPA, 1979b).

PAH which contain more than three rings (such as benz(a)-anthracene) are relatively stable in the environment, and may be transported in air and water by adsorption to particulate matter. However, biodegradation and chemical treatment are effective in eliminating most PAH in the environment.

The reader is referred to the PAH Hazard Profile for a more general discussion of PAH (U.S. EPA, 1979c).

II. EXPOSURE

A. Water

Benz(a)anthracene levels in surface waters or drinking water have not been reported. However, the concentration of six representative PAH (not including benz(a)-anthracene) in U.S. drinking water averaged 13.5 ng/l (Basu and Saxena, 1977, 1978).

B. Food

Benz(a)anthracene has been detected in a wide variety of foods including margarine (up to 29.5 ppb), smoked fish (up to 1.7 ppb), yeast (up to 203 ppb), and cooked or smoked meat (up to 33.0 ppb) (U.S. EPA, 1979a). The total intake of all types of PAH through the diet has been estimated at 1.6 to 16 μg/day (U.S. EPA, 1979b). The U.S. EPA (1979a) has estimated the bioconcentration factor for benz(a)anthracene to be 3,100 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficient of benz-(a)anthracene.

C. Inhalation

Benz(a)anthracene has been repeatedly detected in ambient air at concentrations ranging from 0.18 to 4.6 ng/m^3 (U.S. EPA, 1979a). Thus, the human daily intake of benz(a)anthracene by inhalation of ambient air may be in the range of 3.42 to 87.4 ng, assuming that a human breathes 19 m^3 of air per day.

III. PHARMACOKINETICS

There are no data available concerning the pharmacokinetics of benz(a)anthracene, or other PAH, in humans. Nevertheless, it is possible to make limited assumptions based on the results of animal research conducted with several PAH, particularly benzo(a)pyrene.

A. Absorption

The absorption of benz(a)anthracene in humans has not been studied. However, it is known (U.S. EPA, 1979a) that, as a class, PAH are well-absorbed across the respiratory and gastrointestinal epithelia. In particular, benz(a)-anthracene was reported to be readily transported across the gastrointestinal mucosa (Rees, et al., 1971). The high lipid solubility of compounds in the PAH class supports this observation.

B. Distribution

The distribution of benz(a)anthracene in mammals has not been studied. However, it is known (U.S. EPA, 1979a) that other PAH are widely distributed throughout the body following their absorption in experimental rodents. Relative to other tissues, PAH tend to localize in body fat and fatty tissues (e.g., breast).

C. Metabolism

Benz(a)anthracene, like other PAH, is metabolized by the microsomal mixed-function oxidase enzyme system in mammals (U.S. EPA, 1979b). Metabolic attack on one or more of the aromatic double bonds leads to the formation of phenols

and isomeric dihydrodiols by the intermediate formation of reactive epoxides. Dihydrodiols are further metabolized by microsomal mixed-function oxidases to yield diol epoxides, compounds which are known to be biologically reactive intermediates for certain PAH. Removal of activated intermediates by conjugation with glutathione or glucuronic acid, or by further metabolism to tetrahydrotetrols, is a key step in protecting the organism from toxic interaction with cell macromolecules.

D. Excretion

The excretion of benz(a)anthracene by mammals has not been studied. However, the excretion of closely related PAH is rapid and occurs mainly via the feces (U.S. EPA, 1979a). Elimination in the bile may account for a significant percentage of administered PAH. However, the rate of disappearance of various PAH from the body and the principal routes of excretion are influenced both by the structure of the parent compound and the route of administration (U.S. EPA, 1979a). It is unlikely that PAH will accumulate in the body with chronic low-level exposures.

IV. EFFECTS

A. Carcinogenicity

Benz(a)anthracene is recognized as a weak carcinogen in mammals (U.S. EPA, 1979a,b). It is a tumor initiator on the skin of mice, but failed to yield significant results in the strain A mouse pulmonary tumor bioassay system.

B. Mutagenicity

Benz(a)anthracene has shown weak mutagenic activity in several test system, including Ames Salmonella assay, somatic cells in culture, and sister chromatid exchange in Chinese hamster cells (U.S. EPA, 1979b).

C. Teratogenicity

Pertinent data could not be located in the available literature concerning the possible teratogenicity of benz(a)anthracene. Other related PAH are apparently not significantly teratogenic in mammals (U.S. EPA, 1979a).

D. Other Reproductive Effects

Pertinent data could not be located in the available literature.

E. Chronic Toxicity

The chronic toxicity of benz(a)anthracene has not been extensively studied. The repeated injection of benz(a)anthracene in mice for 40 weeks (total dose, 10 mg.) had little apparent effect on longevity or organ weights (U.S. EPA, 1979b).

V. AQUATIC TOXICITY

A. Acute

Pertinent data could not be located in the available information.

B. Chronic

No standard chronic toxicity data have been presented on freshwater or marine species. The only toxicity data available for benz(a)anthracene for fish is an 87 per-

cent mortality on the freshwater bluegill sunfish, Lepomis macrochirus, exposed to 1,000 µg/l for six months (Brown, et al., 1975).

C. Plant Effects

Pertinent data could not be located in the available information.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human nor the aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have gone through the process of review; therefore, there is a possibility that these criteria will be changed.

A. Human

There are no established exposure criteria for benz(a)anthracene. However, PAH as a class are regulated by several authorities. The World Health Organization (1970) has recommended that the concentration of PAH in drinking water (measured as the total of fluoranthene, benzo(g,h,i)-perylene, benzo(b)fluoranthene, benzo(k)fluoranthene, indeno-(1,2,3-cd)pyrene, and benzo(a)pyrene) not to exceed 0.2 µg/l. Occupational exposure criteria have been established for coke oven emissions, coal tar products, and coal tar pitch volatiles, all of which contain large amounts of PAH including benz(a)anthracene (U.S. EPA, 1979a)..

The U.S. EPA (1979a) draft recommended criteria for PAH in water are based upon the extrapolation of animal carcinogenicity data for benzo(a)pyrene and dibenz(a,h)anthracene.

B. Aquatic

Data were insufficient to propose criteria for freshwater or marine environments.

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No. 18

Benzo(b)fluoranthene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated benzo(b)fluoranthene and has found sufficient evidence to indicate that this compound is carcinogenic.

BENZO(b)FLUORANTHENE

SUMMARY

Benzo(b)fluoranthene is a member of the polycyclic aromatic hydrocarbon (PAH) class. Numerous compounds in the PAH class are well known for their carcinogenic effects in animals. Benzo(b)fluoranthene is carcinogenic to the skin of mice and produces sarcomas when injected in mice. Very little is known concerning the non-carcinogenic effects produced by chronic exposure to benzo(b)fluoranthene. Although exposure to benzo(b)fluoranthene in the environment occurs in conjunction with exposure to other PAH, it is not known how these compounds may interact in human systems. Furthermore, the specific effects of benzo(b)fluoranthene in humans are not known.

Standard acute or chronic toxicity testing for aquatic organisms has not been found in the available literature.

BENZO(b)FLUORANTHENE

I. INTRODUCTION

This profile is based primarily on the Ambient Water Quality Criteria Document for Polynuclear Aromatic Hydrocarbons (U.S. EPA, 1979a) and the Multimedia Health Assessment Document for Polycyclic Organic Matter (U.S. EPA, 1979b).

Benzo(b)fluoranthene ($C_{20}H_{12}$) is one of the family of polycyclic aromatic hydrocarbons (PAH) formed as a result of incomplete combustion of organic material. Its physical/chemical properties have not been well-characterized, other than a reported melting point of 167°C (U.S. EPA, 1979b).

PAH, including benzo(b)fluoranthene, are ubiquitous in the environment, being found in ambient air, food, water, soils, and sediment (U.S. EPA, 1979b). The PAH class contains a number of potent carcinogens (e.g., benzo(a)pyrene), moderately active carcinogens (e.g., benzo(b)fluoranthene), weak carcinogens (e.g., benz(a)anthracene), and cocarcinogens (e.g., fluoranthene), as well as numerous noncarcinogens (U.S. EPA, 1979b).

PAH which contain more than three rings (such as benzo-(b)fluoranthene) are relatively stable in the environment and may be transported in air and water by adsorption to particular matter. However, biodegradation and chemical treatment are effective in eliminating most PAH in the environment. Refer to the PAH Hazard Profile (U.S. EPA, 1979c) for a more general treatment of PAH.

II. EXPOSURE

A. Water

In a monitoring survey of U.S. drinking water, Basu and Saxena (1977, 1978) were unable to detect benzo(b)fluoranthene. However, the concentration of six representative PAH (fluoranthene, benzo(a)pyrene, benzo(g h i)perylene, benzo(j)fluoranthene, benzo(k)fluoranthene, indeno(1,2,3-cd) pyrene) averaged 13.5 ng/l.

B. Food

Levels of benzo(b)fluoranthene have not been reported for food. However, the total intake of all types of PAH through the diet has been estimated at 1.6 to 16 µg/day (U.S. EPA, 1979b). The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor of benzo(b)fluoranthene to be 6,800 for the edible portion of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficient of benzo(b)fluoranthene.

C. Inhalation

Benzo(b)fluoranthene has been detected in ambient air at concentrations ranging from 0.1 to 1.6 ng/m^3 (Gordon and Bryan, 1973). Thus, the human daily intake of benzo(b)-fluoranthene by inhalation of ambient air may be in the range of 1.9 to 30.4 ng, assuming that a human breathes 19 m^3 of air per day.

III. PHARMACOKINETICS

Pertinent data could not be located in the available literature concerning the pharmacokinetics of benzo(b)fluoranthene, or other PAH, in humans. Nevertheless, it is pos-

sible to make limited assumptions based on the results of animal research conducted with several PAH, particularly benzo(a)pyrene.

A. Absorption

The absorption of benzo(b)fluoranthene in humans or other animals has not been studied. However, it is known (U.S. EPA, 1979a) that, as a class, PAH are well-absorbed across the respiratory and gastrointestinal epithelia. The high lipid solubility of compounds in the PAH class supports this observation.

B. Distribution

The distribution of benzo(b)fluoranthene in mammals has not been studied. However, it is known (U.S. EPA, 1979a) that other PAH are widely distributed throughout the body following their absorption in experimental rodents. Relative to other tissues, PAH tend to localize in body fat and fatty tissues (e.g., breast).

C. Metabolism

The metabolism of benzo(b)fluoranthene in mammals has not been studied. Benzo(b)fluoranthene, like other PAH, is most likely metabolized by the microsomal mixed-function oxidase enzyme system in mammals (U.S. EPA, 1979b). Metabolic attack on one or more of the aromatic double bonds leads to the formation of phenols and isomeric dihydrodiols by the intermediate formation of reactive epoxides. Dihydrodiols are further metabolized by microsomal mixed-function oxidases to yield diol epoxides, compounds which are known to be biologically reactive intermediates for certain PAH. Removal of activated intermediates by conjugation with gluta-

thione or glucuronic acid, or by further metabolism to tetrahydrotetrols, is a key step in protecting the organism from toxic interaction with cell macromolecules.

D. Excretion

The excretion of benzo(b)fluoranthene by mammals has not been studied. However, the excretion of closely related PAH is rapid and occurs mainly via the feces (U.S. EPA, 1979a). Elimination in the bile may account for a significant percentage of administered PAH. It is unlikely that PAH will accumulate in the body with chronic low-level exposures.

IV. EFFECTS

A. Carcinogenicity

Benzo(b)fluoranthene is regarded as a moderately active carcinogen (U.S. EPA, 1979b). It is carcinogenic by skin painting on mice, and by subcutaneous injection in mice (U.S. EPA, 1979b; LaVoie, et al. 1979). The sarcomagenic potency of benzo(b)fluoranthene is similar to that of benzo(a)pyrene (Buu-Hoi, 1964).

B. Mutagenicity

Benzo(b)fluoranthene is mutagenic in the Ames Salmonella assay in the presence of a microsomal activating system (LaVoie, et al. 1979). It is also positive in the induction of sister-chromatid exchanges by intraperitoneal injection in Chinese hamsters (U.S. EPA, 1979b).

C. Teratogenicity

Pertinent data could not be located in the literature available concerning the possible teratogenicity of

benzo(b)fluoranthene. Other related PAH are apparently not significantly teratogenic in mammals (U.S. EPA, 1979a).

D. Other Reproductive Effects

Pertinent information could not be located in the available literature.

E. Chronic Toxicity

Published data are not available regarding the non-carcinogenic chronic effects of benzo(b)fluoranthene. It is known, however, that exposure to carcinogenic PAH may produce widespread tissue damage as well as selective destruction of proliferating tissues (e.g., hematopoietic and lymphoid systems) (U.S. EPA, 1979a).

V. AQUATIC TOXICITY

Pertinent information could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

There are no established exposure criteria for benzo(b)fluoranthene. However, PAH as a class are regulated by several authorities. The World Health Organization has recommended that the concentration of PAH in drinking water (measured as the total of fluoranthene, benzo(g,h,i)perylene, benzo(b)fluoranthene, benzo(k)fluoranthene, indeno(1,2,3-cd) pyrene, and benzo(a)pyrene) not exceed 0.2 µg/l. Occupational exposure criteria have been established for coke oven emissions, coal tar products, and coal tar pitch volatiles; all of which contain large amounts of PAH including benzo(b)-fluoranthene (U.S. EPA, 1979a).

The U.S. EPA (1979a) draft recommended criteria for PAH in water are based upon the extrapolation of animal carcinogenicity data for benzo(a)pyrene and dibenzo(a,h)anthracene.

B. Aquatic

The criteria for freshwater and marine life have not been drafted (U.S. EPA, 1979a).

BENZO(b)FLUORANTHENE

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Basu, D.K. and J. Saxena. 1977. Analysis of raw and drinking water samples for polynuclear aromatic hydrocarbons. U.S. Environ. Prot. Agency, P.O. No. CA-7-2999-A. Exposure Evaluation Branch, HERL, Cincinnati, Ohio.

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No. 19

Benzo(a)pyrene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
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APRIL 30, 1980

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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated benzo(a)pyrene and has found sufficient evidence to indicate that this compound is carcinogenic.

BENZO(a)PYRENE

Summary

The first chemicals shown to be involved in the development of cancer belong to the polynuclear aromatic hydrocarbons (PAH) class. Benzo(a)pyrene is the most widely recognized and extensively studied of all carcinogenic PAH. It is among the most potent animal carcinogens known and produces tumors in virtually all species by all routes of administration.

Since humans are never exposed to only benzo(a)pyrene in the environment, it is not possible to attribute human cancers solely to exposure to benzo(a)pyrene. However, numerous epidemiologic studies support the belief that carcinogenic PAH, including benzo(a)pyrene, are also human carcinogens.

Measured steady-state bioconcentration factors are not available for freshwater or saltwater aquatic species exposed to benzo(a)pyrene. Standard toxicity data for freshwater and saltwater aquatic life have not been reported.

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Polynuclear Aromatic Hydrocarbons (U.S. EPA, 1979a) and the Multimedia Health Assessment Document for Polycyclic Organic Matter (U.S. EPA, 1979b).

Benzo(a)pyrene ($C_{20}H_{12}$) is one of the family of polynuclear aromatic hydrocarbons (PAH) formed as a result of incomplete combustion of organic material. Its physical and chemical properties have not been well-characterized, other than a reported melting point of 178.8-179.3°C and a vapor pressure of 5.49×10^{-9} mm Hg (U.S. EPA, 1979b).

PAH, including benzo(a)pyrene, are ubiquitous in the environment, being found in ambient air, food, water, soils and sediment (U.S. EPA, 1979a). The PAH class contains a number of potent carcinogens (e.g., benzo(a)pyrene), moderately active carcinogens (e.g., benzo(b)fluoranthene), weak carcinogens (e.g., benz(a)anthracene), and cocarcinogens (e.g., fluoranthene), as well as numerous noncarcinogens (U.S. EPA, 1979a).

PAH which contain more than three rings (such as benzo(a)pyrene) are relatively stable in the environment and may be transported in air and water by adsorption to particulate matter. However, biodegradation and chemical treatment are effective in eliminating most PAH in the environment.

II. EXPOSURE

A. Water

Basu and Saxena (1977, 1978) have monitored various United States drinking water supplies for the presence of PAH, including benzo(a)pyrene. They reported that the average level of benzo(a)pyrene in drinking water was 0.55 nanograms/liter. This would result in a human daily intake of benzo(a)pyrene from water of about 0.0011 µg.

B. Food

Benzo(a)pyrene has been detected in a wide variety of foods by numerous investigators (U.S. EPA, 1979a). Benzo(a)pyrene levels are especially high in cooked or smoked meats, where in certain cases (i.e., charcoal-broiled steak) concentrations as high as 50 ppb have been reported (Lijinsky and Ross, 1967). It has been estimated (U.S. EPA, 1979b) that the daily dietary intake of benzo(a)pyrene is about 0.16 to 1.6 µg, and total PAH intake is about 1.6 to 16 µg. The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor for benzo(a)pyrene to be 6,800 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficient for benzo(a)pyrene.

C. Inhalation

Benzo(a)pyrene levels have been routinely monitored in the ambient atmosphere for many years. The average urban-rural ambient benzo(a)pyrene concentration in the United States has been estimated at 0.5 nanograms/m^3 (U.S. EPA, 1979a). Thus, the human daily intake of benzo(a)pyrene by inhalation of ambient air is about 9.5 nanograms, assuming that a human breathes about 19 m^3 of air per day.

III. PHARMACOKINETICS

Pertinent data could not be found in available literature concerning the pharmacokinetics of benzo(a)pyrene, or other PAH, in humans. Nevertheless, it is possible to make limited assumptions based on the results of animal research conducted with several PAH, particularly benzo(a)pyrene.

A. Absorption

Toxicity data indicate that, as a class, PAH are capable of passage across epithelial membranes (Smyth, et al. 1962). In particular, benzo(a)-pyrene was reported to be readily transported across the intestinal mucosa

(Rees, et al. 1971) and the respiratory membranes (Kotin, et al. 1969; Vainick, et al. 1976).

B. Distribution

Benzo(a)pyrene becomes localized in a wide variety of body tissues following its absorption (Kotin, et al. 1969). Due to its high lipid solubility, benzo(a)pyrene localizes primarily in body fat and fatty tissues (e.g., breast) (Schlede, et al. 1970a,b).

C. Metabolism

The metabolism of benzo(a)pyrene in mammals has been studied in great detail (U.S. EPA, 1979a). Benzo(a)pyrene, like other PAH, is metabolized by the microsomal mixed function oxidase enzyme system in mammals (U.S. EPA, 1979b). Metabolic attack on one or more of the aromatic rings leads to the formation of phenols and isomeric dihydrodiols by the intermediate formation of reactive epoxides. Dihydrodiols are further metabolized by microsomal mixed function oxidases to yield diol epoxides, compounds which are known to be ultimate carcinogens for certain PAH. Removal of activated intermediates by conjugation with glutathione or glucuronic acid, or by further metabolism to tetrahydrotetrols, is a key step in protecting the organism from toxic interaction with cell macromolecules.

D. Excretion

The excretion of benzo(a)pyrene by mammals has been studied by several groups of investigators. In general, the excretion of benzo(a)pyrene and related PAH is rapid, and occurs mainly via the feces (U.S. EPA, 1979a; Schlede, et al. 1970a,b). Elimination in the bile may account for a significant percentage of administered PAH. It is unlikely that PAH will accumulate in the body as a result of chronic low-level exposures.

IV. EFFECTS

A. Carcinogenicity

The carcinogenic activity of benzo(a)pyrene was first recognized decades ago, and since that time it has become a laboratory standard for the production of experimental tumors which resemble human carcinomas in animals. The carcinogenic activity of benzo(a)pyrene is distinguished by several remarkable features: (1) it is among the most potent animal carcinogens known, producing tumors by single exposures to microgram quantities; (2) it acts both at the site of application and at organs distant to the site of absorption; and (3) its carcinogenicity has been demonstrated in nearly every tissue and species tested, regardless of the route of administration (U.S. EPA, 1979a).

Oral administration of benzo(a)pyrene to rodents can result in tumors of the forestomach, mammary gland, ovary, lung, liver, and lymphoid and hematopoietic tissues (U.S. EPA, 1979a). Exposure to benzo(a)pyrene by intratracheal instillation in rodents can also be an effective means of producing respiratory tract tumors (Feron, et al. 1973). In addition, benzo-(a)pyrene has remarkable potency for the induction of skin tumors in mice by direct dermal application (U.S. EPA, 1979a).

Numerous epidemiologic studies support the belief that carcinogenic PAH, including benzo(a)pyrene, are responsible for the production of human cancers both in occupational situations and among tobacco smokers (U.S. EPA, 1979b).

B. Mutagenicity

Benzo(a)pyrene gives positive results in nearly all mutagenicity test systems including the Ames Salmonella assay, cultured Chinese hamster cells, the sister-chromatid exchange test, and the induction of DNA repair synthesis (U.S. EPA, 1979a).

C. Teratogenicity and Other Reproductive Effects

Only limited data are available regarding the teratogenic effects of benzo(a)pyrene or other PAH in animals. Benzo(a)pyrene had little effect on fertility or the developing embryo in several mammalian and non-mammalian species (Rigdon and Rennels, 1964; Rigdon and Neal, 1965).

D. Chronic Toxicity

As long ago as 1937, investigators knew that carcinogenic PAH such as benzo(a)pyrene produced systemic toxicity as manifested by an inhibition of body growth in rats and mice (Haddow, et al., 1937). The target organs affected by chronic administration of carcinogenic PAH are diverse, due partly to extensive distribution in the body and also to the selective destruction of proliferating cells (e.g., hematopoietic and lymphoid system, intestinal epithelium, testis) (Philips, et al. 1973).

V. AQUATIC TOXICITY

Pertinent data could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

There are no established exposure standards specifically for benzo(a)pyrene. However, PAH as a class are regulated by several authorities. The World Health Organization (1970) has recommended that the concentration of PAH in drinking water (measured as the total of fluoranthene, benzo(g,h,i)perylene, benzo(b)fluoranthene, benzo(k)fluoranthene, indeno(1,2,3-cd)pyrene, and benzo(a)pyrene) not exceed 0.2 µg/l. Occupational exposure cri-

teria have been established for coke oven emissions, coal tar products, and coal tar pitch volatiles, all of which contain large amounts of PAH in water based upon the extrapolation of animal carcinogenicity data for benzo(a)pyrene and dibenz(a,h)anthracene. Levels for each compound are derived which will result in specified risk levels of human cancer as shown in the table below:

BaP

Exposure Assumptions (per day)	Risk Levels and Corresponding Draft Criteria			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams of fish and shellfish.	0	0.097	0.97	9.7
Consumption of fish and shellfish only.		0.44	4.45	44.46

DBA

Exposure Assumptions (per day)	Risk Levels and Corresponding Draft Criteria			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams of fish and shellfish.	0	0.43	4.3	43
Consumption of fish and shellfish only.		1.96	19.6	196

B Aquatic

Guidelines are not available for benzo(a)pyrene in aquatic environments.

BENZO(A)PYRENE

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No. 20

Benzotrichloride

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

BENZOTRICHLORIDE

Summary

Benzotrichloride has been shown to be mutagenic in a number of microbial tests with and without metabolic activation. One study has described the carcinogenicity of benzotrichloride in mice. The lowest concentration producing a lethal effect (LC_{LO}) has been reported at 125 ppm for rats inhaling benzotrichloride for four hours. Pertinent data for the toxic effects to aquatic organisms were not found in the available literature.

I. INTRODUCTION

Benzotrichloride (CAS registry number 98-07-7), is a colorless, oily, fuming liquid. It is made by the free radical chlorination of boiling toluene (Sidi, 1964; Windholz, 1976). Benzotrichloride has the following physical and chemical properties (Windholz, 1976; Sidi, 1964):

Formula:	$C_6H_5Cl_3$
Molecular Weight:	195.48
Melting Point:	-5°C
Boiling Point:	220.8°C
Density:	1.3756^{20}_{4}
Solubility:	alcohol, ether, benzene, insoluble in water

Benzotrichloride is used extensively in the dye industry for the production of Malachite green, Rosamine, Quinoline red, and Alizarine yellow A. It can also be used to produce ethyl orthobenzoate (Sidi, 1964).

II. EXPOSURE

A. Water

Benzotrichloride decompose in the presence of water to benzoic and hydrochloric acids (Windholz, 1976).

B. Food

Pertinent data were not found in the available literature.

C. Inhalation

Pertinent data were not found in the available literature; however, significant exposure could occur in the workplace from accidental spills. Benzotrichloride decomposes in moist air to benzoic and hydrochloric acids (Windholz, 1976).

D. Dermal

Benzotrichloride is irritating to the skin (Windholz, 1976).

III. PHARMACOKINETICS

Pertinent pharmacokinetic data were not found in the available literature.

IV. EFFECTS

A. Carcinogenicity

In a study by Matsushito and coworkers (1975), benzotrichloride was found to induce carcinomas, leukemia, and papillomas in mice. The details of the study were not available for assessment.

B. Mutagenicity

Yasuo, et al. (1978) tested the mutagenicity of several compounds including benzotrichloride in microbial systems such as the rec-assay using Bacillus subtilis, reversion assays using E. coli, and the Ames assay using Salmonella typhimurium, with or without metabolic activation. Benzotrichloride was positive for mutagenicity in the rec-assay and was highly positive on certain strains of E. coli and S. typhimurium in the reversion assay with metabolic activation. Without metabolic activation, however, benzotrichloride was only weakly positive in the latter assay.

C. Teratogenicity, Reproductive Effects, and Chronic Toxicity

Pertinent data were not found in the available literature.

D. Acute Toxicity

The lowest lethal concentration (LC_{LO}) for rats inhaling benzotrichloride is 125 ppm for four hours (Smyth, et al. 1951).

Benzotrichloride was severely irritating to the skin of rabbits that received dermal applications of 10 mg for 24 hours and to the eyes of rabbits that received instillations of 50 µg to the eye (Smyth, et al. 1951).

V. AQUATIC TOXICITY

Pertinent data were not found in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

Existing guidelines and standards were not found in the available literature.

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No. 21

Benzyl Chloride

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

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BENZYL CHLORIDE

Summary

Benzyl chloride has been shown to produce carcinogenic effects in rats following subcutaneous administration and in mice following intraperitoneal administration.

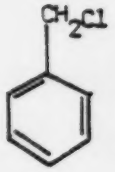
Weak mutagenic activity of the compound has been demonstrated in the Ames Salmonella assay and in E. coli.

There is no available information on the possible teratogenic or adverse reproductive effects of benzyl chloride.

Inhibition of cell multiplication in the alga, Microcystis aeruginosa, started at 30 mg/l. Concentrations of 10 mg/l and 17 mg/l caused paralysis in two species of fish.

I. INTRODUCTION

Benzyl chloride (alpha-chlorotoluene), CAS Registry number 100-44-7, is a colorless-to-light yellow, clear, lachrymatory liquid and is made by free-radical (photochemical) chlorination of tolene (Hawley, 1971; Austin, 1974). It has the following physical and chemical properties (Windholz, et al. 1976; Hawley, 1971; Weast, 1972):



Formula:	C_7H_7Cl
Molecular Weight:	126.59
Melting Point:	-43°C
Boiling Point:	179°C
Density:	1.100^{20}_{20}
Solubility:	Miscible in alcohol, chloroform, ether; insoluble in water
Production:	approximately 89 million lbs. 1977 (NIOSH, 1977)

Benzyl chloride is a moderately volatile compound with a vapor pressure of 1 mm Hg at 22°C (NIOSH, 1978). The compound decomposes relatively slowly in water with a 15-hour half-life of pH 7 (25°C) (NIOSH, 1978).

Benzyl chloride is used to make benzaldehyde through additional chlorination and hydrolysis, but modest amounts are also used as a benzylating agent for benzyl benzoate, n-butyl benzyl phthalate, benzyl ethyl aniline, benzyl cellulose, components of dyes and perfumes, and for production of phenylacetic acid by benzyl cyanide (Austin, 1974).

II. EXPOSURE

A. Water

Gruber (1975) reports that no benzyl chloride enters the water from production.

B. Food

Pertinent data could not be located in the available literature.

C. Inhalation

Pertinent data were not found in the available literature; however, benzyl chloride is used exclusively as a chemical intermediate in manufacturing and exposure and is most likely limited to the workplace. As such, the level of exposure is reported to be less than 1 ppm (NIOSH, 1978).

D. Dermal

Pertinent data could not be located in the available literature.

III. PHARMACOKINETICS

A. Absorption and Distribution

Pertinent data could not be located in the available literature.

B. Metabolism and Excretion

The major excretion product following ingestion of benzyl chloride is a cysteine conjugate, benzylmercapturic acid (Stekol, 1938, 1939; Witter, 1944; Barnes, et al. 1959; Knight and Young, 1958).

Bray, et al. (1958) administered benzyl chloride at 200 mg/kg body weight orally to rabbits. Urine collected for 24 hours showed 86.4 percent of the administered dose in the soluble fraction, with 49 percent as benzylmercapturic acid, 20 percent as a glycine conjugate, 0.4 percent as glucosiduronic acid, and 17 percent as unconjugated benzoic acid. Maitrya and Vyas (1970) found 30 percent of the total oral dose of benzyl chloride to be excreted by rats as hippuric acid.

Knight and Young (1958) found that benzyl chloride is converted directly to benzyl mercapturic acid, unlike related compounds such as chlorinated benzenes, which form acid-labile precursors.

Barnes, et al. (1959) found that 27 percent of the total oral dose of benzyl chloride administered to rats was excreted as benzyl mercapturic acid. This value compares with 49 percent excreted in rabbits (Bray, et al. 1958) and 4 percent in guinea pigs (Bray, et al. 1959).

Several studies have indicated that glutathione is the source of the thiol groups for mercapturic acid formation from benzyl chloride (Barnes, et al. 1959; Simkin and White, 1957; Anderson and Mosher, 1951; Waelsch and Rittenberg, 1942; Bray, et al. 1969; Beck, et al. 1964). The turnover rate of glutathione in the liver was found to be 49 mg/100 g of liver per hour (Simkin and White, 1957). An in vitro study by Suga, et al. (1966) revealed that conjugation with glutathione can occur both enzymatically and non-enzymatically in rat liver preparations. The enzymic conjugation has also been observed in human liver preparations (Boyland and Chasseaud, 1969).

IV. EFFECTS

A. Carcinogenicity

Benzyl chloride was reviewed by IARC (1976) and found to be carcinogenic in rats. Druckrey, et al. (1970) injected 14 rats subcutaneously with benzyl chloride at 2.1 g/kg body weight (total dose) and 8 rats with 3.9 g/kg body weight (total dose) during 51 weeks. Injection site sarcomas were noted in three of the rats receiving the lower dose and six receiving the higher dose; most of the tumors had metastasized to the lungs. The vehicle of administration, arachis oil, did not produce local tumors.

Poirier, et al. (1975) administered intraperitoneal injections of benzyl chloride in tricaprylin to three groups of 20 male and female A/Heston mice, three times per week for eight weeks, with total doses of 0.6, 1.3, and 2.0 g/kg body weight. After 24 weeks, all survivors were killed;

lung tumors occurred in 4/15, 7/16, and 2/8 surviving mice in the three groups, respectively. The average number of tumors per mouse was 0.26, 0.50, and 0.25, respectively. The incidence of tumors in mice receiving the benzyl chloride was not significantly different from the results recorded for untreated mice on the tricaprylin-vehicle treated mice.

B. Mutagenicity

McCann, et al. (1975a,b) found benzyl chloride to be weakly mutagenic (less than 0.10 revertants/nanomole) when tested using the Ames assay (Salmonella/microsomal activation).

Rosenkranz and Poirier (1978), in a National Cancer Institute report, found benzyl chloride to be marginally mutagenic in the Ames assay at doses of 5 µl and 10 µl/plate without activation. Microsomal activation had an inactivating effect on benzyl chloride. The investigators also evaluated the DNA-modifying activity in bacterial systems using Escherichia coli pol A mutants. A dose of 10 µl benzyl chloride produced a positive mutagenic effect.

Benzyl chloride was found to be non-mutagenic in the Ames Salmonella microsomal assay by Simmon (1979). The compound was mutagenic when exposure was by vapor phase in a dessicator.

C. Teratogenicity, Other Reproductive Effects and Chronic Toxicity

Pertinent data could not be located in the available literature.

D. Acute Toxicity

A number of studies have been conducted on the acute toxicity of benzyl chloride vapor to animals and were reviewed in a criteria document prepared by NIOSH (1978). Respiratory tract inflammation and secondary infections were observed in mice exposed to 390 mg/m^3 (LC_{50}) for two hours and rats exposed to 740 mg/m^3 (LC_{50}) for two hours (Mikhailova, 1965).

Rabbits exposed to 480 mg/m^3 of benzyl chloride for eight hours/day for six days suffered mild eye and nasal irritation by the sixth day, while cats exposed to the same regimen suffered a loss of appetite in addition to eye and respiratory tract irritation (Wolf, 1912). Death of a dog occurred within 24 hours of exposure to 1,900 mg/m^3 of benzyl chloride for eight hours. Corneal turbidity and irritation of the ocular, respiratory, and oral mucosa were observed before death (Schutte, 1915). Mikhailova (1965) observed hepatic changes and necrosis of the kidney in rats and mice exposed to benzyl chloride at 100 mg/m^3.

Landsteiner and Jacobs (1936) investigated the sensitizing properties of benzyl chloride to guinea pigs. Benzyl chloride, in a saline solution (0.01 mg/animal) was injected intracutaneously twice per week for 12 weeks. Two weeks later, re-exposure revealed that benzyl chloride had a sensitizing effect.

Occupational exposures to benzyl chloride have been reported by several investigators (Wolf, 1912; Schutte, 1915; Mikhailova, 1971; Katz and Talbert, 1930; Watrous, 1947). Lacrimination, conjunctivitis, and irritation of the respiratory tract and eyes have been reported following exposure to benzyl chloride vapor levels ranging from 6 to 8 mg/m^3 for five minutes to brief exposure at 23,600 mg/m^3. Although no cases were reported in the literature, liquid benzyl chloride has the potential for skin irritation based on its release of hydrochloric acid upon hydrolysis. The odor threshold and nasal irritation thresholds for benzyl chloride are 0.21 to 0.24 mg/m^3 and 180 mg/m^3, respectively (Katz and Talbert, 1930; Leonardos, et al. 1969).

V. AQUATIC TOXICITY

A. Acute and Chronic Toxicity

Pertinent data could not be located in the available literature.

B. Plant Effects

Inhibition of cell multiplication in Microcystis aeruginosa started at 30 mg/l (Bringmann and Kuhn, 1976).

C. Residues

Pertinent data could not be located in the available literature.

D. Other Relevant Information

Hiatt, et al. (1953) found that 1.0 mg/l of benzyl chloride produced no irritant response in marine fish, but 10 mg/l caused a slight irritant activity. This compound caused paralysis in the fish Trutta iridea and Cyprinus carpio at concentrations of 10 mg/l and 17 mg/l, respectively (Meinck, et al. 1970).

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The American Conference of Governmental and Industrial Hygienists (ACGIH, 1977) recommends an occupational exposure limit of 1 ppm (5 mg/m^3) for benzyl chloride. The U.S. federal standard promulgated by OSHA is also 1 ppm (TWA) (29 CFR 1910.1000). NIOSH recommends an environmental exposure limit of 5 mg/m^3 as a ceiling value for a 15-minute exposure (NIOSH, 1978).

B. Aquatic

No guidelines to protect fish and saltwater organisms from benzyl chloride toxicity have been established because of the lack of available data.

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No. 22

Beryllium

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated beryllium and has found sufficient evidence to indicate that this compound is carcinogenic.

BERYLLIUM

SUMMARY

Beryllium was shown to be carcinogenic in three animal species, producing cancers of the lung and bone when administered by injection, inhalation, or intratracheal instillation. Ingestion of beryllium has failed to produce cancers in animals, possibly due to its poor gastrbintestinal absorption. Several epidemiology studies support the hypothesis that beryllium is a human carcinogen.

Beryllium is toxic to freshwater organisms at concentrations as low as 5.3 µg/l. Pertintent data for marine organisms were not found in the available literature (U.S. EPA, 1979).

BERYLLIUM

I. INTRODUCTION

This profile is primarily based upon the Ambient Water Quality Criteria Document for Beryllium (U.S. EPA, 1979). Recent comprehensive reviews on the hazards of beryllium have also been prepared by the National Institute for Occupational Safety and Health (NIOSH, 1972) and the International Agency for Research on Cancer (IARC, 1972).

Beryllium (Be; atomic weight 9.01) is a dark gray metal of the alkaline earth family. Beryllium has the following physical-chemical properties (IARC, 1972):

Boiling point:	2970°C
Melting point:	1284 - 1300°C
Hardness:	60 - 125
Density:	1.84 - 1.85
Solubility:	Soluble in acids and alkalis

World production of beryllium was reported as approximately 250 tons annually, but much more reaches the environment as emissions from coal burning operations (Tepper, 1972). Most common beryllium compounds are readily soluble in water. The hydroxide is soluble only to the extent of 2 mg/l (Lange, 1956). Beryllium forms chemical compounds in which its valence is +2. At acid pH, it behaves as a cation but forms anionic complexes at pH greater than 8 (Krejci and Scheel, 1966). The major source of beryllium in the environment is the combustion of fossil fuels (Tepper, 1972). Beryllium enters the waterways through weathering of rocks and soils, through atmospheric fallout and through discharges from industrial and municipal operations.

II. EXPOSURE

A. Water

Kopp and Kroner (1967) reported the results of trace metal analyses of 1,577 drinking water samples obtained throughout the United States. Beryllium was detected in 5.4 percent of the samples. Concentrations ranged from 0.01 to 1.22 µg/l, with a mean value of 0.19 µg/l.

B. Food

Beryllium has been detected in a variety of vegetables, and in eggs, milk, nuts, bread, and baker's yeast (Meehan and Smythe, 1967; Petzow and Zorn, 1974). Measured levels of beryllium were generally in the range of 0.01 to 0.5 ppm. Using the data for consumption and bioconcentration for freshwater and saltwater fishes, mollusks, and decapods, and the measured steady-state bioconcentration factor (BCF) for beryllium in bluegills, the U.S. EPA (1979) has estimated a weighted average BCF for beryllium to be 19 for the edible portions of fish and shellfish consumed by Americans.

C. Inhalation

The detection of beryllium in air is infrequent and usually in trace amounts. In urban areas beryllium levels may reach 0.008 µg/m^3, while in rural areas beryllium concentrations have been measured at 0.00013 µg/m^3 (Tabor and Warren, 1958; National Air Sampling Network, 1968). At a beryllium extraction plant in Ohio, beryllium concentrations were generally around 2 µg/m^3 over a seven year period (Breslin and Harris, 1959).

III. PHARMACOKINETICS

Ingested beryllium is poorly absorbed within the gastrointestinal tract, presumably due to solubility problems in the alimentary canal (Hyslop, et al. 1943; Reeves, 1965). When inhaled, soluble beryllium compounds are rapidly removed from the lung, whereas insoluble beryllium compounds can remain in the lung indefinitely (Van Cleave and Kaylor, 1955; Wagner, et al. 1969; Sprince, et al. 1976). When parenterally administered, beryllium is distributed to all tissues, although it shows preferential accumulation in bone, followed by spleen, liver, kidney and muscle (Van Cleave and Kaylor, 1955; Crowley, et al. 1949; Klemperer, et al. 1952; Kaylor and Van Cleave, 1953; Spencer, et al. 1972). Absorbed beryllium tends to be either excreted in the urine or deposited in kidneys and bone (Scott, et al. 1950). Once deposited in the skeleton, beryllium is removed very slowly, with half-lives of elimination reported to be 1,210, 890, 1,770 and 1,270 days in mice, rats, monkeys, and dogs, respectively (Furchner, et al. 1973).

IV. EFFECTS

A. Carcinogenicity

Beryllium was shown to be carcinogenic in three animal species. Intravenous injection of beryllium, zinc beryllium silicate, and beryllium phosphate produced osteosarcomas in the rabbit (Gardner and Heslington, 1946; Dutra and Largent, 1950; Komitowski, 1969; Fodor, 1971; IARC, 1972). Inhalation and intratracheal instillation of beryl-

lium compounds have produced lung cancers in the rat and monkey (Vorwald and Reeves, 1959; Vorwald, et al. 1966; Reeves, et al. 1967). Ingestion of beryllium by rats and mice has failed to induce tumors, possibly due to the poor absorption of beryllium from the gastrointestinal tract.

Several epidemiological studies have failed to establish a clear association between beryllium exposure and cancer development (Stoeckle, et al. 1969; Mancuso, 1970; Niemoller, 1963). However, other recent studies support the hypothesis that beryllium is a human carcinogen (Berg and Burbank, 1972; Wagoner, et al. 1978; Discher, 1978).

B. Mutagenicity

Pertinent data were not found in the available literature.

C. Teratogenicity

Beryllium has been implicated as a teratogen in snails (Raven and Sprok, 1953) and has inhibited limb regeneration in the salamander, Amblystoma punctatum (Thorton, 1950).

D. Other Reproductive Effects

Pertinent data were not found in the available literature.

E. Chronic Toxicity

Chronic beryllium inhalation in humans produces a progressive, systemic disease which may follow the cessation of exposure by as long as five years (Tepper, et

al. 1961; Hardy and Stoeckle, 1959). Symptoms include pneumonitis with cough, chest pain, and general weakness. Systemic effects include right heart enlargement with cardiac failure, enlargement of liver and spleen, cyanosis, digital clubbing, and kidney stones (Hall, et al. 1959). Chronic beryllium disease can be produced in rats and monkeys by inhalation of beryllium sulfate at 35 $\mu g/m^3$ (Schepers, et al. 1957; Vorwald, et al. 1966).

V. AQUATIC TOXICITY

A. Acute Toxicity

Acute toxicity data for beryllium for freshwater fishes are taken from 22 static and 5 flow-through bioassays, all 96 hours in duration. U.S. EPA (1979) presents the most sensitive species, the guppy Poecilia reticulata, with LC_{50} values ranging from 71 to 17,500 µg/l. The data reflect that the toxicity of beryllium to freshwater fish is decreased in hard water. This has also been confirmed by U.S. EPA (1979) in the fathead minnow, Pimephales promelas, with LC_{50} values ranging from 82 to 11,000 µg/l. Acute toxicity for aquatic invertebrates provides two 48-hour LC_{50} values of 7,900 and 2,500 µg/l, with water hardness values of 180 and 200 µg/l as $CaCo_3$. The source of these invertebrate studies is the same for chronic freshwater studies. No data for acute toxicity to marine species was found in the available literature.

B. Chronic Toxicity

No chronic tests for freshwater fish were found in the available literature. The cladoceran, Daphnia magna, was the only freshwater species tested for chronic effects; chronic values of less than 36 µg/l and 5.3 µg/l were obtained by the U.S. EPA (1979). No chronic data for marine species of fish or invertebrates was found in the available literature.

C. Plant Effects

The only plant study available reveals that the green algae, Chlorella vannieli, displayed growth inhibition at a concentration of 100,000 µg/l (U.S. EPA, 1979).

D. Residues

Exposure of the bluegill for 28 days produced a bioconcentration factor of 19 (U.S. EPA, 1978). No other data was found in the available literature.

E. Other Relevant Information

The only marine data presented showed reduced alkaline phosphatase activity in the mummichog, Fundulus heteroclitus, at concentrations as low as 9 ug/l. A teratogenic response was observed by Evola-Maltese (1957) in sea urchin embryos at concentrations of 9.010 µg/l.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The present standard for occupational exposure to beryllium prescribes an 8-hour time-weighted average

of 2.0 $\mu g/m^3$ with a ceiling concentration of 5.0 $\mu g/m^3$. This is the same value recommended by the American Conference of Governmental Industrial Hygienists (1977). The National Institute for Occupational Safety and Health (NIOSH, 1972) recommends that occupational exposure to beryllium and its compounds not exceed 1 $\mu g/m^3$ (8-hour time-weighted average) with a ceiling limit of 5 $\mu g/m^3$ (measured over a 15 minute sampling period).

National Emission Standards for Hazardous Air Pollutants set their criterion as not more than 10 g in 24 hours or emissions which result in maximum outplant concentrations of 0.01 $\mu g/m^3$, 30-day average (U.S. EPA, 1977).

Based on animal bioassay data for beryllium to which the linear model was applied, the U.S. EPA (1979) has estimated levels of beryllium in ambient water which will result in carcinogenic risk for humans. As a result of the public comments received, additional review and reevaluation of the data base is required before a final criterion level can be recommended.

B. Aquatic

The U.S. EPA proposed a water quality standard of 11 $\mu g/l$ for the protection of aquatic life in soft freshwater; 1,100 $\mu g/l$ for the protection of aquatic life in hard freshwater; and 100 $\mu g/l$ for continuous irrigation on all soils, except 500 mg/l for irrigation on neutral to alkaline lime-textured soils (U.S. EPA, 1977).

The National Academy of Science/National Academy of Engineering (1973) Water Quality Criteria recommendation for marine aquatic life is: hazard level - 1.5 µg/l; minimal risk of deleterious effects - 0.1 mg/l; and application factor - 0.01 (applied to 96-hour LC_{50}). Their recommendation for irrigation water is: 0.10 mg/l for continuous use on all soils.

The U.S. EPA (1979) has derived a draft criterion for beryllium to protect freshwater aquatic organisms. The 24-hour average concentration in µg/l is dependent on water hardness and is derived by the following equation:

$$CR = e^{(1.24 \ln (\text{hardness}) - 6.65)}$$

The concentration not to be exceeded at any time is:

$$CR = e^{(1.24 \ln (\text{hardness}) - 1.46)}$$

No draft criterion was derived for marine organisms (U.S. EPA, 1979).

BERYLLIUM

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No. 23

Bis(2-chloroethoxy)methane

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

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BIS(2-CHLOROETHOXY)METHANE

Summary

Pertinent data could not be located in the available literature searches on the mutagenic, carcinogenic, teratogenic, or adverse reproductive effects of bis(2-chloroethoxy)methane (BCEXM) in mammals. A closely related compound, bis(2-chloroethoxy)ethane (BCEXE) has been shown to produce skin tumors and injection site sarcomas in animal studies.

Pertinent information could not be located in the available literature on bis(2-chloroethoxy)methane toxicity to aquatic organisms.

BIS(2-CHLOROETHOXY)METHANE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Chloroalkyl Ethers (U.S. EPA, 1979a).

The chloroalkyl ethers are compounds in which a hydrogen atom in one or both of the aliphatic ether chains are substituted with chlorine. Bis(2-chloroethoxy)methane (BCEXM, dichloroethyl formal, $ClCH_2CH_2-O-CH_2-OCH_2-CH_2Cl$) is a colorless liquid at room temperature with a boiling point of 218.1°C and a specific gravity of 1.2339. The compound is slightly soluble in water but miscible with most organic solvents.

The chloroalkyl ethers have a wide variety of industrial uses in organic synthesis, treatment of textiles, the manufacture of polymers and insecticides, as degreasing agents and solvents, and in the preparation of ion exchange resins (U.S. EPA, 1979a).

The chloroalkyl ethers, like BCEXM, have a higher stability in water than the alpha chloroalkyl ethers, which decompose. BCEXM is decomposed by mineral acids.

II. EXPOSURE

No specific information on exposure to BCEXM is available. The reader is referred to a more general treatment of chloroalkyl ethers (U.S. EPA, 1979b). BCEXM has been monitored in rubber plant effluents at a maximum level of 140 mg/l (Webb, et al. 1973). Bis-1,2-(2-chloroethoxy)ethane (BCEXE), a closely related compound, has been reported in drinking water at a maximum level of 0.03 µg/l (U.S. EPA, 1975). Data on levels of BCEXM in foods was not found in the available literature.

No bioaccumulation factor for BCEXM has been derived.

III. PHARMACOKINETICS

Pertinent information could not be located in the available literature on BCEXM. The reader is referred to a more general treatment of chloroalkyl ethers (U.S. EPA, 1979b).

IV. EFFECTS

A. Carcinogenicity

Pertinent information could not be located in the available literature on carcinogenic effects of BCEXM. The reader is referred to a more general treatment of chloroalkyl ethers (U.S. EPA, 1979b). A closely related compound, BCEXE, has been shown to produce skin tumors in mice and injection site sarcomas (Van Duuren, et al. 1972).

B. Mutagenicity, Teratogenicity, Other Reproductive Effects and Chronic Toxicity

Pertinent data could not be located in the available literature for BCEXM.

V. AQUATIC TOXICITY

Pertinent information could not be located in the available literature on the aquatic toxicity of BCEXM.

VI. EXISTING GUIDELINES AND STANDARDS

No standards or recommended criteria exist for the protection of human health or aquatic organisms to bis(2-chloroethoxy)methane.

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No. 24

Bis(2-chloroethyl)ether

Health and Environmental Effects

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WASHINGTON, D.C. 20460

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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated bis(2-chloroethyl)ether and has found sufficient evidence to indicate that this compound is carcinogenic.

BIS(2-CHLOROETHYL)ETHER

Summary

Oral administration of bis(2-chloroethyl)ether (BCEE) did not produce an increase of tumors in rats. Male mice showed a significant increase in hepatomas after ingestion of BCEE. BCEE has also shown activity as a tumor initiator for mouse skin.

Testing of BCEE in the Ames' Salmonella assay, in E. coli, and in Saccharomyces cerevisiae has shown that this compound induces mutagenic effects.

There is no available evidence to indicate that BCEE produces adverse reproductive effects or teratogenic effects.

The data base for bis(2-chloroethyl)ether is limited to three studies. The 96-hr LC_{50} value for the bluegill is reported to be over 600,000 µg/l. Adverse chronic effects were not observed with the fathead minnow at test concentrations as high as 19,000 µg/l. A bioconcentration factor of 11 was observed during a 14-day exposure of bluegills. The half-life was 4-7 days.

BIS(2-CHLOROETHYL)ETHER

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Chloralkyl Ethers (U.S. EPA, 1979a).

The chloroalkyl ethers are compounds in which a hydrogen atom in one or both of the aliphatic ether chains are substituted with chlorine. Bis(2-chloroethyl)ether (BCEE, molecular weignt 143.01) is a colorless liquid at room temperature with a boiling point of 176-178°C at 760 mm Hg, and a density of 1.213. The compound is practically insoluble in water, but is miscible with most organic solvents (U.S. EPA, 1979a).

The chloroalkyl ethers have a wide variety of industrial and laboratory uses in organic synthesis, in textile treatment, the manufacture of polymers and insecticides, as degreasing agents, and in the preparation of ion exchange resins (U.S. EPA, 1979a).

The B-substituted chloroalkyl ethers, such as BCEE, are generally more stable and hence less reactive in aqueous systems than the a-substituted compounds (U.S. EPA, 1979a).

For additional information regarding chloroalkyl ethers in general, the reader is referred to the EPA/ECAO Hazard Profile on Chloroalkyl Ethers (U.S. EPA 1979b).

II. EXPOSURE

The B-chloroalkyl ethers have been monitored in water. Industrial discharges from chemical plants involved in the manufacture of glycol products, rubber, and insecticides may contain high levels of BCEE (U.S. EPA, 1979a). The highest concentration of BCEE in drinking water reported by the U.S. EPA

(1975) is 0.5 µg/l. There is no evidence of the occurrence of the chloroalkyl ethers in the atmosphere; human exposure appears to be confined to occupational settings.

Human exposure to chloroalkyl ethers via ingestion of food is unknown (U.S. EPA, 1979a). The B-chloroalkyl ethers, due to their stability and low water solubility, may have a high tendency to be bioaccumulated. The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor for BCEE to be 25 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on a measured steady-state bioconcentration factor using bluegills.

III. PHARMACOKINETICS

A. Absorption

Experiments with radiolabelled BCEE have indicated that the compound is readily absorbed following oral administration (Lingg, et al. 1978). Information on inhalation or dermal absorption of chloroalkyl ethers is not available (U.S. EPA, 1979a).

B. Distribution

Pertinent information on the distribution of BCEE could not be located in the literature.

C. Metabolism

The biotransformation of BCEE in rats following oral administration appears to involve cleavage of the ether linkage and subsequent conjugation with non-protein-free sulfhydryl groups, the major route, or with glucuronic acid (Lingg, et al. 1978). Thiodiglycolic acid and 2-chloroethanol-B-O-glucuronide were identified as urinary metabolites of BCEE in rats.

D. Excretion

BCEE administered to rats by intubation was eliminated rapidly in the urine, with more than 60 percent of the compound excreted within 24 hours (Lingg, et al. 1978).

IV. EFFECTS

A. Carcinogenicity

BCEE has shown activity as a tumor initiator in mouse skin (U.S. EPA, 1979a). Preliminary results of an NCI study indicate that oral administration of BCEE does not produce an increase in tumor incidence in rats (U.S. EPA, 1979a); however, mice administered BCEE by ingestion showed a significant increase in hepatomas (Innes, et al. 1969).

B. Mutagenicity

Testing of the chloroalkyl ethers in the Ames' Salmonella assay and in E. coli have indicated that BCEE induces mutagenic effects (U.S. EPA, 1979a). BCEE has also shown mutagenic effects in Saccharomyces cerevisiae (Simmon, et al. 1977), but none were found in the heritable translocation test for mice (Jorgenson, et al. 1977).

C. Teratogenicity, Chronic Toxicity and other Reproductive Effects

Pertinent information could not be located in the available literature.

D. Other Relevant Information

Acute physiological responses of the guinea pig to innalation of high concentrations of BCEE were congestion, emphysema, edema and hemorrhage of the lungs (Shrenk, et al. 1933). Brief exposure of man to BCEE vapor, at levels 260 ppm, irritated the nasal passages and eyes with profuse lacrimation. Deep innalation produced nausea. The highest concentration with no noticeable effect was 35 ppm (Shrenk, et al. 1933).

V. AQUATIC TOXICITY

A. Acute Toxicity

96-hr LC_{50} value for the bluegill, Lepomis macrochirus, could not be determined for bis(2-chloroethyl)ether with exposure concentrations as high as 600,000 µg/l (U.S. EPA, 1978).

B. Chronic Toxicity

An embryo-larval test has been reported with bis(2-chloroethyl) ether and the fathead minnow, Pimephales promelas. Adverse effects were not observed at test concentrations as high as 19,000 µg/l (U.S. EPA, 1978).

C. Plant Effects

Pertinent data could not be located in the available literature.

D. Residues

A bioconcentration factor of 11 was determined during a 14-day exposure of bluegills to bis(2-chloroethyl)ether. The half-life was 4-7 days.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979a) which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

Based on the results of an animal carcinogenesis bioassay, and using a linear, non-threshold model, the U.S. EPA (1979a) has estimated that an ambient water level of 0.42 µg/l will present an increased risk of 10^{-5} or less for BCEE, assuming water and the injection of contaminated aquatic organisms to be the only sources of exposure.

The 8-hour, time-weighted average threshold limit value (TLV-TWA) for BCEE determined by the American Conference of Governmental Industrial Hygienists (ACGIH, 1978) is 5 ppm for BCEE.

B. Aquatic

Freshwater or saltwater criteria cannot be derived for bis(2-chloroethyl)ether because of insufficient data (U.S. EPA, 1979a).

BIS(2-CHLOROETHYL)ETHER

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No. 25

Bis(2-Chloroisopropyl)ether

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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BIS(2-CHLOROISOPROPYL)ETHER

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Chloroalkyl Ethers (U.S. EPA, 1979a).

The chloroalkyl ethers are compounds in which a hydrogen atom in one or both of the aliphatic ether chains are substituted with chlorine. Bis(2-chloroisopropyl)ether (BCIE, molecular weight 171.07) is a colorless liquid at room temperature with a boiling point of 187-188°C at 760 mm Hg. The compound is practically insoluble in water but is miscible with organic solvents.

The chloroalkyl ethers have a wide variety of industrial and laboratory uses in organic synthesis, treatment of textiles, the manufacture of polymers and insecticides, as degreasing agents, and in the preparation of ion exchange resins (U.S. EPA, 1979a).

The beta-chloroalkyl ethers, like BCIE, are more stable in aqueous system than the alpha-chloroalkyl ethers, which decompose rapidly. For additional information regarding the chloroalkyl ethers as a class, the reader is referred to the Hazard Profile on Chloroalkyl Ethers (U.S. EPA, 1979b).

II. EXPOSURE

The beta-chloroalkyl ethers have been monitored in water. Industrial discharges from chemical plants involved in the manufacture of glycol products, rubber, and insecticides may present high effluent levels (U.S. EPA, 1979a). The highest concentration of BCIE monitored in drinking water by the U.S. EPA (1975) was reported as 1.58 µg/l.

The concentrations of chloroalkyl ethers in foods have not been monitored. The beta-chloroalkyl ethers, however, due to their relative stability and low water solubility, may have a high tendency to be bioaccumulated.

BIS(2-CHLOROISOPROPYL)ETHER

Summary

Preliminary results from an NCI carcinogenesis bioassay do not show an increase in tumors following oral administration of bis(2-chloroisopropyl)-ether (BCIE).

BCIE has produced mutagenic effects in two bacterial test systems (Salmonella and E. coli) but has failed to show mutagenicity in one mammalian study.

No information is available on the teratogenic or adverse reproductive effects of BCIE.

Chronic exposure to BCIE has produced liver damage in animals.

Data on the toxicity of bis(2-chloroisopropyl)ether to aquatic organisms are not available.

The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor for bis(2-chloroisopropyl)ether to be 106 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficient.

III. PHARMACOKINETICS

A. Absorption

Experiments with radio-labeled BCIE have indicated that the compound is readily absorbed following oral administration (Smith, et al. 1977). No information on inhalation or dermal absorption of the chloroalkyl ethers is available (U.S. EPA, 1979a).

B. Distribution

Species differences in the distribution of radio-labeled BCIE have been reported by Smith, et al. (1977). Monkeys retained higher amounts of radioactivity in the liver, muscle, and brain than did rats. Urine and expired air from monkeys also contained higher levels of radioactivity than those determined in the rat. Blood levels of BCIE in monkeys reached a peak within 2 hours following oral administration and then declined in a biphasic manner (t 1/2 = 5 hours and 2 days, respectively).

C. Metabolism

Urinary metabolites of labeled BCIE identified in studies with rats included 1-chloro-2-propanol, propylene oxide, 2-(1-methyl-2-chloro-ethoxy) propionic acid, and carbon dioxide (Smith, et al. 1977).

D. Excretion

Smith, et al. (1977) found that in the rat, 63.36 percent, 5.87 percent, and 15.96 percent of a 30 mg orally-administered dose of BCIE were recovered after 7 days in the urine, feces, and expired air, respectively. In the monkey, the corresponding figures were 28.61 percent, 1.19 percent, and 0 percent, respectively.

IV. EFFECTS

A. Carcinogenicity

Preliminary results of an NCI carcinogenicity bioassay indicate that oral administration of BCIE does not produce an increase in tumor incidence (U.S. EPA, 1979a).

B. Mutagenicity

Testing of BCIE in the Ames Salmonella assay and in E. coli have indicated that the compound shows mutagenic activity (U.S. EPA, 1979a). BCIE did not show mutagenic effects in the murine heritable translocation test (Jorgenson, et al. 1977).

C. Teratogenicity and Other Reproductive Effects

Pertinent data could not be located in the available literature.

D. Chronic Toxicity

Chronic oral exposures of mice to BCIE produced centrilobular liver necrosis in mice. The major effects in rats were pulmonary congestion and pneumonia (U.S. EPA, 1979a).

E. Other Relevant Information

Several chloroalkyl ethers show initiating activity and therefore may interact with other agents to produce skin papillomas (Van Duuren, et al. 1969, 1972); however, data specific to BCIE is not available.

V. AQUATIC TOXICITY

Pertinent data could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

BCIE is an isomer of a group of chloroalkyl ethers which have been shown to have carcinogenic potential. BCIE has been shown to be mutagenic; however, definitive proof of carcinogenicity has not been demonstrated. The available data is presently under review and a definitive determination as to the carcinogenicity of this isomer cannot be made at this time.

B. Aquatic

No draft criteria to protect fish and saltwater aquatic organisms from bis(2-chloroisopropyl)ether toxicity have been derived (U.S. EPA, 1979).

BIS(2-CHLOROISOPROPYL)ETHER (BCIE)

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No. 26

Bis(Chloromethyl)ether

Health and Environmental Effects

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WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated bis(chloromethyl)ether and has found sufficient evidence to indicate that this compound is carcinogenic.

BIS(CHLOROMETHYL)ETHER

Summary

Bis(chloromethyl)ether (BCME) has been shown to produce tumors in animals following administration by subcutaneous injection, inhalation, or dermal application. Epidemiological studies of workers in the United States, Germany, and Japan who were exposed to BCME and chloromethyl methyl ether (CMME) indicate that these compounds are human respiratory carcinogens.

BCME has produced mutagenic effects in the Ames' Salmonella assay and in E. coli. Increased cytogenetic abnormalities have been observed in the lymphocytes of workers exposed to BCME and CMME; this effect appeared to be reversible.

There is no available evidence to indicate that the chloroalkyl ethers produce adverse reproductive effects or teratogenic effects.

Information has not been found on the toxicity of bis(chloromethyl) ether to aquatic organisms. The hazard profiles on the haloethers and the chloroalkyl ethers should be consulted for the toxicity of related compounds.

BIS(CHLOROMETHYL)ETHER

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Chloroalkyl Ethers (U.S. EPA, 1979a).

The chloroalkyl ethers are compounds in which hydrogen atoms in one or both of the aliphatic ether chains are substituted with chlorine. Bis-(chloromethyl)ether, (BCME; molecular weight 115.0), is a colorless liquid at room temperature with a boiling point of 104°C at 760 mm Hg, and a density of 1.328. The compound immediately hydrolyzes in water, but is miscible with ethanol, ether, and many organic solvents (U.S. EPA, 1979a).

The chloroalkyl ethers have a wide variety of industrial and laboratory uses in organic synthesis, textile treatment, the manufacture of polymers and insecticides, the preparation of ion exchange resins, and as degreasing agents (U.S. EPA, 1979a).

While BCME is very unstable in water, it appears to be relatively stable in the atmosphere (Tou and Kallos, 1974). Spontaneous formation of BCME occurs in the presence of both hydrogen chloride and formaldehyde (Frankel, et al. 1974). For additional information regarding the chloroalkyl ethers in general, the reader is referred to the EPA/ECAO Hazard Profile on Chloroalkyl Ethers (U.S. EPA, 1979b).

II. EXPOSURE

As might be expected from the reactivity of BCME in water, monitoring studies have not detected its presence in water. Human exposure by innalation appears to be confined to occupational settings (U.S. EPA, 1979a).

Data for human exposure to chloroalkyl ethers by ingestion of food is not available, nor is data relevant to human dermal exposure to chloralkyl ethers (U.S. EPA, 1979a).

The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor for BCME to be 31 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficient.

III. PHARMACOKINETICS

There is no specific information relating to the absorption, distribution, metabolism, or excretion of BCME (U.S. EPA, 1979a). Because of the high reactivity and instability of BCME in aqueous systems, it is difficult to generate pharmacokinetic parameters.

IV. EFFECTS

A. Carcinogenicity

BCME has been shown to produce tumors in several animal systems. Inhalation exposure of male rats to BCME produced malignant respiratory tract tumors (Kuschner, et al. 1975), while dermal application to mouse skin led to the appearance of skin tumors (Van Duuren, et al. 1968). Administration of BCME to newborn mice by ingestion has been shown to increase the incidence of hepatocellular carcinomas in males (Innes, et al. 1969).

Epidemiological studies of workers in the United States, Germany, and Japan who were occupationally exposed to BCME and CMME have indicated that these compounds are human respiratory carcinogens (U.S. EPA, 1979a).

BCME has been shown to accelerate the rate of lung tumor formation in strain A mice following inhalation exposure (Leong, et al. 1971). BCME has also shown activity as a tumor initiating agent for mouse skin (Slaga, et al. 1973).

B. Mutagenicity

Testing of the chloroalkyl ethers in the Ames Salmonella assay and in E. coli have indicated that BCME produced direct mutagenic effects (U.S. EPA, 1979a).

The results of a study on the incidence of cytogenetic aberrations in the lymphocytes of workers exposed to BCME and CCME indicate higher frequencies in this cohort. Follow-up indicates that removal of workers from exposure led to a decrease in the frequency of aberrations (Zudova and Landa, 1977).

C. Teratogenicity and Other Reproductive Effects

Pertinent data could not be located in the available literature regarding teratogenicity and other reproductive effects.

D. Chronic Toxicity

Chronic occupational exposure to CMME contaminated with BCME has produced bronchitis in workers (U.S. EPA, 1979a). Cigarette smoking has been found to act synergistically with this type of exposure to produce bronchitis (Weiss, 1976, 1977).

E. Other Relevant Information

The initiating activity of several chloroalkyl ethers indicates that these compounds will interact with other agents to produce skin papillomas (Van Duuren, et al. 1969, 1972).

V. AQUATIC TOXICITY

Pertinent information could not be found in the available literature regarding aquatic toxicity for freshwater or marine species.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979a) which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

Based on animal carcinogenesis data, and using a linear, non-threshold model, the U.S. EPA (1979a) has recommended a maximum permissible

concentration of BCME for ingested water at .02 ng/l. Assuming water is the only source of exposure, compliance to this level should limit the risk carcinogenesis to not more than 10^{-5}.

Based on animal studies, the 8-hour, time-weighted threshold limit value (TLV-TWA) has been recommended for BCME as one ppb by the American Conference of Governmental and Industrial Hygienists (1978).

8. Aquatic

Criterion for the protection of freshwater or marine aquatic organisms were not drafted due to lack of toxicological evidence.

BIS(CHLOROMETHYL) ETHER

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No. 27

Bis(2-ethylexyl)phthalate

Health and Environmental Effects

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APRIL 30, 1980

DISCLAIMER

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BIS-(2-ETHYLHEXYL)PHTHALATE

SUMMARY

Bis-(2-ethylhexyl)phthalate has been shown to produce mutagenic effects in the Ames Salmonella assay and in the dominant lethal assay.

Teratogenic effects in rats were reported following interperitoneal (i.p.) administration and oral administration of bis-(2-ethylhexyl)phthalate. Additional reproductive effects produced by bis-(2-ethylhexyl)phthalate include impaired implantation and parturition, and decreased fertility in rats. Testicular damage and decreased spermatogenesis have been reported in rats, following i.p. or oral administration, and in mice, given bis-(2-ethylhexyl)phthalate by oral intubation.

Evidence has not been found indicating that bis-(2-ethylhexyl)phthalate has carcinogenic effects. Chronic animal feeding studies of bis-(2-ethylhexyl)phtnalate have shown effects on the liver and kidneys.

Bis-(2-ethylhexyl)phthalate is acutely toxic to freshwater invertebrates at a concentration of 11,000 µg/l. The same species has been shown to display severe reproductive impairment when exposed to concentrations less than 3 µg/l.

BIS-(2-ETHYLHEXYL) PHTHALATE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Phthalate Esters (U.S. EPA, 1979).

Bis-(2-ethylhexyl)phthalate, most commonly referred to as di-(2-ethylhexyl)phthalate, (DEHP) is a diester of the ortho form of benzene dicarboxylic acid. The compound has a molecular weight of 391.0, specific gravity of 0.985, boiling point of 386.9°C at 5 mm Hg, and is insoluble in water (U.S. EPA, 1979).

DEHP is widely used as a plasticizer, primarily in the production of polyvinyl chloride (PVC) resins. As much as 60 percent by weight of PVC materials may be plasticizer (U.S. EPA, 1979). Through this usage, DEHP is incorporated into such products as wire and cable covering, floor tiles, swimming pool liners, upholstery, and seat covers, footwear, and food and medical packaging materials (U.S International Trade Commission, 1978).

In 1977, current production was 1.94×10^5 tons/year (U.S. EPA, 1979).

Phthalates have been detected in soil, air, and water samples; in animal and human tissues; and in certain vegetation. Evidence from in vitro studies indicates that certain bacterial flora may be capable of metabolizing phthalates to the monoester form (Englehardt, et al. 1975).

II. EXPOSURE

Phthalate esters appear in all areas of the environment. Environmental release of the phthalates may occur through leaching of plasticizers from PVC materials, volatilization of phthalates from PVC materials, and the incineration of PVC items. Sources of human exposure to phthalates include contaminated foods and fish, and parenteral administration by use of PVC blood bags, tubings, and infusion devices (U.S. EPA, 1979).

Monitoring studies have indicated that phthalate concentrations in water are mostly in the ppm range, or 1-2 µg/liter (U.S. EPA, 1979). Air levels of phthalates in closed rooms that have PVC tiles have been reported to be 0.15 to 0.26 mg/m^3 (Peakall, 1975). Industrial monitoring has measured air levels of phthalates from 1.7 to 66 mg/m^3 (Milkov, et al. 1973). Levels of DEHP have ranged from not detectable to 68 ppm in foodstuffs (Tomita, et al. 1977). Cheese, milk, fish and shellfish present potential sources of high phthalate intake (U.S. EPA, 1979). Estimates of parenteral exposure of patients to DEHP during use of PVC medical appliances have indicated approximately 150 mg DEHP exposure from a single hemodialysis course. An average of 33 mg DEHP exposure is possible during open heart surgery (U.S. EPA, 1979).

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for DEHP to be 95 for the edible portions of fish and shellfish consumed by Americans. This

estimate is based on the measured steady-state bioconcentration studies in fathead minnow.

III. PHARMACOKINETICS

A. Absorption

The phthalates are readily absorbed from the intestinal tract, the peritoneal cavity, and the lungs (U.S. EPA, 1979). Daniel and Bratt (1974) found that seven days following oral administration of radiolabelled DEHP, 42 percent of the dose was recovered in the urine and 57 percent recovered in the feces of rats. Bilary excretion of orally administered DEHP has been noted by Wallin, et al. (1974). Limited human studies indicate that 2 to 4.5 percent of orally administered DEHP was recovered in the urine of volunteers within 24 hours (Shaffer, et al. 1945). Lake, et al. (1975) have suggested that orally administered phthalates are absorbed after metabolic conversion to the monoester form in the gut.

Dermal absorption of DEHP in rabbits has been reported at 16 to 20 percent of the initial dose within three days following administration (Autian, 1973).

B. Distribution

Studies in rats injected with radiolabelled DEHP have shown that 60 to 70 percent of the administered dose was detected in the liver and lungs within 2 hours after administration (Daniel and Bratt, 1974). Wadell, et al. (1977) have reported rapid accumulation of labelled DEHP in the kidney and liver of rats after i.v. injection, followed by rapid excretion into the urine, bile, and intes-

tine. Seven days after i.v. administration of labelled DEHP to mice, levels of compound were found preferentially in the lungs and to a lesser extent in the brain, fat, heart, and blood (Autian, 1973).

An examination of tissue samples, from two deceased patients who had received large volumes of transfused blood, detected DEHP in the spleen, liver, lungs, and abdominal fat (Jaeger and Rubin, 1970).

Injection of pregnant rats with labelled DEHP has shown that the compound may cross the placental barrier (Singh, et al. 1975).

C. Metabolism

Various metabolites of DEHP have been identified following oral feeding to rats (Albro, et al. 1973). These results indicate that DEHP is initially converted from the diester to the monoester, followed by the oxidation of the monoester side chain forming two different alcohols. The alcohols are oxidized to the corresponding carboxylic acid or ketone. Enzymatic cleavage of DEHP to the monoester may take place in the liver or the gut (Lake, et al. 1977). This enzymatic conversion has been observed in stored whole blood indicating widespread distribution of metabolic activity (Rock, et al. 1978).

D. Excretion

Excretion of orally administered DEHP is virtually complete in the rat within 4 days (Lake, et al. 1975). Major excretion is through the urine and feces, with biliary

excretion increasing the content of DEHP (or metabolites) in the intestine (U.S. EPA, 1979). Schulz and Rubin (1973) have noted an increase in total water soluble metabolites of labelled DEHP in the first 24 hours following injection into rats. Within one hour, eight percent of the DEHP was found in the liver, intestines and urine. After 24 hours, 54.6 percent was recovered in the intestinal tract, excreted feces and urine, and only 20.5 percent was recovered in organic extractable form. Blood loss of DEHP showed a biphasic pattern, with half-lives of 9 minutes and 22 minutes, respectively (Schulz and Rubin, 1973).

IV. EFFECTS

A. Carcinogenicity

Pertinent data could not be located in the available literature.

B. Mutagenicity

Testing of DEHP in the Ames Salmonella assay has shown no mutagenic effects (Rubin, et al. 1979). Yagi, et al. (1978) have indicated that DEHP is not mutagenic in a recombinant strain of Bacillus, but the monoester metabolite of DEHP did show some mutagenic effects. Results of a dominant lethal assay in mice indicate that DEHP has a dose and time dependent mutagenic effect (Singh, et al. 1974).

C. Teratogenicity

DEHP has been shown to produce teratogenic effects in rats following i.p. administration (Singh, et al. 1972).

Following oral administration there was a significant reduction in fetus weight at 0.34 and 1.70 g/kg/day.

D. Other Reproductive Effects

Effects on implantation and parturition have been observed in pregnant rats injected intraperitoneally with DEHP (Peters and Cook, 1973). A three-generation reproduction study in rats has indicated decreased fertility in rats following maternal treatment with DEHP (Industrial Bio-Test, 1978).

Testicular damage has been reported in rats administered DEHP i.p. or orally. Seth, et al. (1976) found degeneration of the seminiferous tubules and changes in spermatagonia; testicular atrophy and morphological damage were noted in rats fed DEHP (Gray, et al. 1977; Yamada, et al, 1975). Otake, et al. (1977) noted decreased spermatogenesis in mice administered DEHP by intubation.

E. Chronic Toxicity

Oral feeding of DEHP produced increases in liver and kidney weight in several animal studies (U.S. EPA, 1979). Chronic exposure to transfused blood containing DEHP has produced liver damage in monkeys (Kevy, et al. 1978). Lake, et al. (1975) have produced liver damage in rats by administration of mono-2-ethylhexyl phthalate.

F. Other Relevant Information

Several animal studies have demonstrated that pre-treatment of rats with DEHP produced an increase in hexobarbital sleeping times (Daniel and Bratt, 1974; Rubin and Jaeger, 1973; Swinyard, et al. 1976).

V. AQUATIC TOXICITY

A. Acute Toxicity

Only one acute study on the freshwater cladoceran (Daphnia magna) has produced a 96-hour static LC_{50} value of 11,000 µg/l (U.S. EPA, 1978). Freshwater fish or marine data have not been found in the literature.

B. Chronic Toxicity

Chronic studies involving the rainbow trout (Salmo gairdneri) provided a chronic value of 4.2 µg/l in an embryo-larval assay (Mehrle and Mayer, 1976). Severe reproductive impairment was observed at less than 3 µg/l in a chronic Daphnia magna assay (Mayer and Sanders, 1973).

C. Plant Effects

Pertinent information could not be located in the available literature.

D. Residues

Bioconcentration factors have been obtained for several species of freshwater organisms: 54 to 2,680 for the scud (Gamarus pseudolimnaeus); 14 to 50 for the sowbug (Ascellus brevicaudus); 42 to 113 for the rainbow trout (Salmo gairdneri); and 91 to 886 for the fathead minnow (Pimephales promelas) (U.S. EPA, 1979).

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

Based on "no effect" levels observed in chronic feeding studies in rats or dogs, the U.S. EPA has calculated an acceptable daily intake (ADI) level for DEHP of 42 mg/day.

The recommended water quality criteria level for protection of human health is 10 mg/l for DEHP (U.S. EPA, 1979).

B. Aquatic

Criterion was not drafted for either freshwater or marine environments due to insufficient data.

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No. 28

Bromoform

Health and Environmental Effects

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APRIL 30, 1980

DISCLAIMER

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BROMOFORM

SUMMARY

Bromoform has been detected in finished drinking water in the United States and Canada. It is believed to be formed by the haloform reaction that may occur during water chlorination. Bromoform can be removed from drinking water via treatment with activated carbon. Natural sources (especially red algae) produce significant quantities of bromoform. There is a potential for bromoform to accumulate in the aquatic environment because of its resistance to degradation. Volatilization is likely to be an important means of environmental transport.

Bromoform gave positive results in mutagenicity tests with Salmonella typhimurium TA100. In a short-term in vivo oncogenicity assay it caused a significant increase in tumor incidence at one dose level.

Inhalation of bromoform by humans can cause irritation of the respiratory tract and liver damage. Respiratory failure is the primary cause of death in bromoform-related fatalities.

I. INTRODUCTION

This profile is based primarily on the Ambient Water Quality Criteria document for halomethanes (U.S. EPA 1979b).

Bromoform (tribromomethane; $CHBr_3$) is a colorless, heavy liquid similar in odor and taste to chloroform. Bromoform has the following physical/chemical properties (Weast, 1974):

Molecular Weight:	252.75
Melting Point:	8.3'C
Boiling Point:	149.5'C (at 760 mm Hg)
Vapor Pressure:	10 mm Hg al 34'C
Solubility:	slightly soluble in water; soluble in a variety of organic solvents.

A review of the production range (includes importation) statistics for bromoform (CAS No. 75-25-2) which is listed in the initial TSCA Inventory (1979a) has shown that between 100,000 and 900,000 pounds of this chemical were produced/imported in 1977.*/

Bromoform is used as a chemical intermediate; solvent for waxes, greases, and oils; ingredient in fire-resistant chemicals and gauge fluids (U.S. EPA 1978a; Hawley, 1977).

II. EXPOSURE

A. Environmental Fate

Bromoform gradually decomposes on standing; air and light accelerate decomposition (Windholz, 1976). The vapor pressure of bromoform, while lower than that for chloroform and other chloroalkanes, is, nonetheless, sufficient to ensure that volatilization will be an important means of environmental transport. The

*/ This production range information does not include any production/importation data claimed as confidential by the person(s) reporting for the TSCA Inventory, nor does it include any information which would compromise Confidential Business Information. The data submitted for the TSCA Inventory, including production range information, are subject to the limitations contained in the Inventory Reporting Regulations (40 CFR 710).

half-life for hydrolysis of bromoform is estimated at 686 years. Bromoform should be much more reactive in the atmosphere. Oxidation by HO radical will result in a half-life of a few months in the troposphere (U.S. EPA, 1977).

B. Bioconcentration

The bioconcentration factor for bromoform in aquatic organisms that contain about 8% lipid is estimated to be 48. The weighted average bioconcentration factor for bromoform in the edible portion of all aquatic organisms consumed by Americans is estimated to be 14 (U.S. EPA, 1979b).

C. Environmental Occurence

The National Organics Reconnaissance Survey detected bromoform in the finished drinking water of 26 of 80 cities, with a maximum concentration of 92 ug/l. Over 90% of the samples contained 5 ug/l or less. No bromoform was found in raw water samples (Symons et al., 1975). Similarly, the EPA Region V Organics Survey found bromoform in 14% of the finished drinking water samples and none in raw water (U.S. EPA, 1975). Using a variety of sampling and analysis methods, the National Organic Monitoring Survey found bromoform in 3 of 111, 6 of 118, 38 of 113, 19 of 106, and 30 of 105 samples with mean concentrations ranging from 12-28 ug/l (U.S. EPA, 1978b). A Canadian survey of drinking water found 0-0.2 ug/l with a median concentration of 0.01 ug/l (Health and Welfare Can., 1977).

The National Academy of Sciences (1978) concluded that water chlorination, via the haloform reaction, results in the production of trihalomethanes (including bromoform) from the organic precursors present in raw water.

Significant quantities of bromoform are also produced from natural sources, especially red algae. For example, the essential oil of Asparagopsis taxiformis (a red marine algae eaten by Hawaiians) contains approximately 80% bromoform (Burreson et al., 1975).

III. PHARMACOKINETICS

Bromoform is absorbed through the lungs, gastrointestinal tract, and skin. Some of the absorbed bromoform is metabolized in the liver to inorganic bromide ion. Bromide is found in tissues and urine following inhalation or rectal administration of bromoform (Lucas, 1929). Metabolism of bromoform to carbon monoxide has also been reported (Ahmed, 1977). Recent studies show that phenobarbital-induced rats metabolize bromoform to carbonyl bromide ($COBr_2$), the brominated analog of phosgene ($COCl_2$) (Pohl et al., 1979).

IV. HEALTH EFFECTS

A. Carcinogenicity

Bromoform caused a significant increase in tumor incidence at one dose level in a short-term in vivo oncogenicity assay known as the strain A mouse lung adenoma test. The increase was observed at a dose of 48 mg/kg/injection with a total dose of 1100 mg/kg. The tumor incidence was not increased significantly at doses of 4 mg/kg (total dose of 72 mg/kg) or 100 mg/kg (total dose of 2400 mg/kg) (Theiss et al., 1977.

B. Mutagenicity

Bromoform was mutagenic in S. typhimurium strain TA 100 (without metabolic activation) (Simmon, 1977).

C. Other Toxicity

Rats inhaling 250 mg/m^3 bromoform for 4 hr/day for 2 months developed impaired liver and kidney function (Dykan, 1962).

In humans, inhalation of bromoform causes irritation to the respiratory tract. Mild cases of bromoform poisoning may cause only headache, listlessness, and vertigo. Unconsciousness, loss of reflexes, and convulsions occur in severe cases. The primary cause of death from a lethal dose of bromoform is respiratory failure. Pathology indicates that the chemical causes fatty degenerative and centrolobular necrotic changes in the liver (U.S. PHS, 1955).

Acute animal studies indicate impaired function and pathological changes in the liver and kidneys of animals exposed to bromoform (Kutob and Plaa, 1962; Dykan, 1962).

V. AQUATIC EFFECTS

A. Fresh Water Organisms

The 96-hr LC_{50} (static) in bluegill sunfish is 29.3 mg/l. The 48-hr LC_{50} (static) for Daphnia magna is 46.5 mg/l. The 96-hr EC_{50}s for chlorophyll A production and cell number in S. capricornutum are 112 mg/l and 116 mg/l, respectively (U.S. EPA, 1978a). (See also Section II.B.)

B. Marine Organisms

The 96-hr LC_{50} (static) in sheepshead minnow is 17.9 mg/l. The 96-hr LC_{50} (static) in mysid shrimp is 20.7 mg/l. The EC_{50}s for chlorophyll A production and cell number in S. costatum are, respectively, 12.3 mg/l and 11.5 mg/l (U.S. EPA, 1978a).

VI. EXISTING GUIDELINES

A. Human

The OSHA standard for bromoform in air is a time weighted average (TWA) of 0.5 ppm (39CFR23540).

The Maximum Contaminant Level (MCL) for total trihalomethanes (including bromoform) in drinking water has been set by the U.S. EPA at 100 ug/l (44FR68624). The concentration of bromoform produced by chlorination can be reduced by treatment of drinking water with powdered activated carbon (Rook, 1974). This is the technology that has been proposed by the EPA to meet this standard.

B. Aquatic

The proposed ambient water criterion for the protection of fresh water aquatic life from excessive bromoform exposure is 840 ug/l as a 24-hour average. Bromoform levels are not to exceed 1900 ug/l at any time. The criterion for the protection of marine life is 180 ug/l (24 hr avg), not to exceed 1900 ug/l (U.S. EPA, 1979b).

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No. 29

Bromomethane

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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BROMOMETHANE

Summary

On acute exposure to bromomethane, neurologic and psychiatric abnormalities may develop and persist for months or years. There is no information on the chronic toxicity, carcinogenicity, or teratogenicity of bromomethane. Bromomethane has been shown to be mutagenic in the Ames S. typhimurium test system.

Acute LC_{50} values have been reported in two tests as 12,000 and 11,000 µg/l for a marine and freshwater fish, respectively.

BROMOMETHANE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Halomethanes (U.S. EPA, 1979a).

Bromomethane (CH_3Br, methyl bromide, monobromomethane, and embafume; molecular weight 94.94) is a colorless gas. Bromomethane has a melting point of -93.6°C, a boiling point of 3.56°C, a specific gravity of 1.676 g/ml at -20°C, and a water solubility of 17.5 g/l at 20°C (Natl. Acad. Sci., 1978). Bromomethane has been widely used as a fumigant, fire extinguisher, refrigerant, and insecticide (Kantarjian and Shaheen, 1963). Today the major use of bromomethane is as a fumigating agent. Bromomethane is believed to be formed in nature, with the oceans as a primary source (Lovelock, 1975). The other major environmental source of bromomethane is from its agricultural use as a soil, seed, feed and space fumigant. For additional information regarding Halomethanes as a class the reader is referred to the Hazard Profile on Halomethanes (U.S. EPA, 1979b).

II. EXPOSURE

A. Water

The U.S. EPA (1975) has identified bromomethane qualitatively in finished drinking waters in the U.S. There are, however, no data on its concentration in drinking water, raw water, or waste water (U.S. EPA, 1979a).

B. Food

There is no information on the concentration of bromomethane in food. Bromomethane residues from fumigation decrease rapidly through loss to the atmosphere and reaction with protein to form

inorganic bromide residues. With proper aeration and product processing, most residual bromomethane will rapidly disappear due to methylation reactions and volatilization (Natl. Acad. Sci., 1978; Davis, et al. 1977). There are no bioconcentration data for bromomethane (U.S. EPA, 1979a).

C. Inhalation

Saltwater atmospheric background concentrations of bromomethane averaging about 0.00036 mg/m^3 have been reported (Grimsrud and Rasmussen, 1975; Singh, et al. 1977). This is higher than reported average continental background and urban levels and suggests that the oceans are a major source of global bromomethane (Natl. Acad. Sci., 1978). Bromomethane concentrations of up to 0.00085 mg/m^3 may occur outdoors locally with light traffic, as a result of exhaust containing bromomethane as a breakdown product of ethylene dibromide, which is used in leaded gasoline (Natl. Acad. Sci., 1978).

III. PHARMACOKINETICS

A. Absorption

Absorption of bromomethane most commonly occurs via the lungs, although it can also occur through the gastrointestinal tract and the skin (Davis, et al. 1977; von Oettingen, 1964).

B. Distribution

Upon absorption, blood levels of residual non-volatile bromide increase, indicating rapid uptake of bromomethane or its metabolites (Miller and Haggard, 1943). Bromomethane is rapidly distributed to various tissues and is broken down to inorganic bromide. Storage, only as bromides, occurs mainly in lipid-rich tissues.

C. Metabolism

Evidently the toxicity of bromomethane is mediated by the bromomethane molecule itself. Its reaction with tissue (methylation of sulfhydryl groups in critical cellular proteins and enzymes) results in disturbance of intracellular metabolic functions, with irritative, irreversible, or paralytic consequences (Natl. Acad. Sci., 1978; Davis, et al. 1977; Miller and Haggard, 1943).

D. Excretion

Elimination of bromomethane is rapid initially, largely through the lungs. The kidneys eliminate much of the remainder as bromide in the urine (Natl. Acad. Sci., 1978).

IV. EFFECTS

Pertinent information relative to the carcinogenicity, teratogenicity or other reproductive effects, or chronic toxcity of bromomethane were not found in the available literature.

A. Mutagenicity

Simmon and coworkers (1977) reported that bromomethane was mutagenic to Salmonella typhimurium strain TA100 when assayed in a dessicator whose atmosphere contained the test compound. Metabolic activation was not required, and the number of revertants per plate was directly dose-related.

B. Other Relevant Information

In several species, acute fatal poisoning has involved marked central nervous system disturbances with a variety of manifestations: ataxia, twitching, convulsions, coma, as well as changes in lung, liver,

heart, and kidney tissues (Sayer, et al. 1930; Irish, et al. 1940; Gorbachev, et al. 1962; von Oettingen, 1964). Also, residual bromide in fumigated food has produced some adverse effects in dogs (Rosenblum, et al. 1960).

V. AQUATIC TOXICITY

Two acute toxicity studies on one freshwater and one marine fish species were reported with LC_{50} values of 11,000 µg/l for freshwater bluegill (Lepomis macrochirus) and an LC_{50} value of 12,000 µg/l for the marine tidewater silversides (Menidia beryllina) (U.S. EPA, 1979a). Pertinent information relative to aquatic chronic toxicity or plant effects for bromomethane were not found in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

The current OSHA standard for occupational exposure to bromomethane (1976) is 80 mg/m^3; the American Conference of Governmental Industrial Hygienist's (ACGIH, 1971) threshold limit value is 78 mg/m^3. The U.S. EPA (1979a) draft water quality criteria for bromomethane is 2 µg/l. Refer to the Halomethane Hazard Profile for discussion of criteria derivation (U.S. EPA, 1979b).

B. Aquatic Toxicity

The draft criterion for protecting freshwater life is a 24-hour average concentration of 140 µg/l, not to exceed 320 µg/l. The marine criterion is 170 µg/l as a 24-hour average, not to exceed 380 µg/l.

BROMOMETHANE

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No. 30

4-Bromophenyl Phenyl Ether

Health and Environmental Effects

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WASHINGTON, D.C. 20460

APRIL 30, 1980

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4-Bromophenyl phenyl ether

SUMMARY

Very little information on 4-bromophenyl phenyl ether exists. 4-Bromophenyl phenyl ether has been identified in raw water, in drinking water and in river water. 4-Bromophenyl phenyl ether has been tested in the pulmonary adenoma assay, a short-term carcinogenicity assay. Although the results were negative, several known carcinogens also gave negative results. No other health effects were available. 4-Bromophenyl phenyl ether appears to be relatively toxic to freshwater aquatic life: a 24-hour average criterion of 6.2 ug/L has been proposed.

I. INTRODUCTION

4-Bromophenyl phenyl ether ($BrC_6H_4OC_6H_5$; molecular weight 249.11) is a liquid at room temperature; it has the following physical/chemical properties (Weast 1972):

Melting point:	18.72°C
Boiling point:	310.14°C (760 mm Hg) 163°C (10 mm Hg)
Density:	1.4208^{20}
Solubility:	Insoluble in water; soluble in ether

No information could be found on the uses of this substance.

A review of the production range (includes importation) statistics for 4-bromophenyl phenyl ether (CAS No. 101-55-3) which is listed in the initial TSCA Inventory (1979) has shown that between 0 and 900 pounds of this chemical were produced/imported in 1977.*

*This production range information does not include any production/importation data claimed as confidential by the person(s) reporting for the TSCA Inventory, nor does it include any information which would compromise confidential business information. The data submitted for the TSCA Inventory, including production range information, are subject to the limitations contained in the Inventory Reporting Regulations (40 CFR 710).

II. EXPOSURE

No specific information relevant to the environmental fate of 4-bromophenyl phenyl ether was found in the literature. A U.S. EPA report (1975a) included this substance in a category with several other drinking water contaminants considered to be refractory to biodegradation (i.e., lifetime greater than two years in unadapted soil; point sources unable to be treated biologically). However, the authors did not present or reference experimental data to support the inclusion of 4-bromopheny phenyl ether in this category. U.S. EPA (1975a) estimated that three tons of 4-bromophenyl phenyl ether are discharged annually.

4-Bromophenyl phenyl ether has been identified as a contaminant in finished drinking water on three occasions, in raw water on one occasion and in river water on one occasion. No quantitative data were supplied (U.S. EPA, 1976). Friloux (1971) and U.S. EPA (1972) have also reported the presence of 4-bromophenyl phenyl ether in raw and finished water of the lower Mississippi River (New Orleans area). Again, no quantitative data were supplied. U.S. EPA (1975) suggest that 4-bromophenyl phenyl ether may be formed during the chlorination of treated sewage and drinking water.

III. PHARMACOKINETICS

No information was located.

IV. HEALTH EFFECTS

A. Carcinogenicity

Three groups of 20 male mice were administered intraperitoneal doses (23, 17 or 18 doses, respectively) of 4-bromophenyl phenyl ether in tricaprylin vehicle three times a week for 8 weeks (Theiss et al. 1977). The total doses were 920, 1700, or 3600 mg/kg, respectively. Animals were sacrificed at 24 weeks from the start of the experiment. Incidences of lung adenomas were not significantly increased, as compared with vehicle controls. However, this short-term assay should not be considered indicative of the nononcogenicity of 4-bromophenyl phenyl ether as several known oncogens tested negative in this assay.

V. AQUATIC TOXICITY

A. Acute

An unadjusted 96 hour LC_{50} of 4,940 ug/L was determined by exposing bluegills to 4-bromophenyl phenyl ether (Table 1). Adjusting this value for test conditions and species sensitivity, a Final Fish Acute Value of 690 ug/L is obtained (U.S. EPA, undated).

Exposure of Daphnia magna, yielded an unadjusted 48 hour LC_{50} of 360 ug/L (Table 2). The Final Invertebrate Acute Value (and the Final Acute Value) for 4-bromophenyl phenyl ether is 14 ug/L (U.S. EPA, undated).

B. Chronic

In an embryo-larval test using the fathead minnow (in which survival and growth were observed), a chronic value of 61 ug/L was obtained for 4-bromophenyl phenyl ether exposure (Table 3). Dividing by the species sensitivity factor (6.7), a Final Fish Chronic Value of 9.1 ug/L is derived. Since no other information is available, this value is also the Final Chronic Value (U.S. EPA, undated).

VI. EXISTING GUIDELINES

A. Aquatic

A 24 hour average concentration of 6.2 ug/L (6.2 ug/L = 0.44 x 14 ug/L (Final Acute Value)) is the recommended criterion to protect freshwater aquatic life. The maximum allowable concentration should not exceed 14 ug/L at any time (U.S. EPA, undated).

Table 1. Freshwater fish acute values

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC_{50} (ug/L)	Adjusted LC_{50} (ug/L)
Bluegill, *Lepomis macrochirus*	S	U	4-Bromophenyl-phenyl ether	96	4,940	2,700

* S = static

** U = unmeasured

Geometric mean of adjusted values: 4-Bromophenylphenyl ether = 2,700 ug/L

$\frac{2,700}{3.9}$ = 690 ug/L

Table 2. Freshwater invertebrate acute values

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC_{50} (ug/L)	Adjusted LC_{50} (ug/L)
Cladoceran, *Daphnia magna*	S	U	4-Bromophenyl-phenyl ether	48	360	300

* S = static

** U = unmeasured

Geometric mean of adjusted values: 4-Bromophenyl phenyl ether = 300 ug/L

$\frac{300}{21}$ = 14 ug/L

Table 3. Freshwater fish chronic values, 4-Bromophenyl phenyl ether

Organism	Test*	Limits (ug/L)	Chronic Value (ug/L)
Fathead minnow, *Pimephales promelas*	E-L	89-167	61

* E-L = embryo-larva

Geometric mean of chronic values = 61 ug/L $\frac{61}{6.7}$ = 9.1 ug/L

Lowest chronic value = 61 ug/L

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No. 31

Cadmium

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated cadmium and has found sufficient evidence to indicate that this compound is carcinogenic.

CADMIUM

Summary

The major non-occupational routes of human cadmium exposure are through food and tobacco smoke. Drinking water also contributes relatively little to the average daily intake.

Epidemiological studies indicate that cadmium exposure may increase the mortality level for cancer of the prostate. Long-term feeding and inhalation studies in animals have not produced tumors, while intravenous administration of cadmium has produced only injection site tumors. Mutagenic effects of cadmium exposure have been seen in animal studies, bacterial systems, in vitro tests, and in the chromosomes of occupationally exposed workers.

Cadmium has produced teratogenic effects in several species of animals, possibly through interference with zinc metabolism. Testicular necrosis and neurobehavioral alterations in animals following exposure during pregnancy have been produced by cadmium in animals.

Chronic exposure to cadmium has produced emphysema and a characteristic syndrome (Itai-Itai disease) following renal damage and osteomalacia. A causal relationship between chronic cadmium exposure and hypertension in humans has been suggested but not confirmed.

Cadmium is acutely toxic to freshwater fish at levels as low as 0.55 µg/l. Freshwater fish embryo/larval stages tended to be the most sensitive to cadmium. Marine fish were generally more resistant than freshwater fish. The long half-life of cadmium in aquatic organisms has been postulated, and severe restrictions to gill-tissue respiration have been observed at concentrations as low as 0.5 µg/l.

CADMIUM

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Cadmium (U.S. EPA, 1979).

Cadmium is a soft, bluish-silver-white metal, harder than tin but softer than zinc. The metal melts at 321°C and shows a boiling point of 765°C (U.S. EPA, 1978b). Cadmium dissolves readily in mineral acids. Some of the physical/chemical properties of cadmium and its compounds are summarized in Table 1 (U.S. EPA, 1978b).

Cadmium is currently used in electroplating, paint and pigment manufacture, and as a stabilizer for plastics (Fulkerson and Goeller, 1973).

Current production: 6000 metric tons (1968) (U.S. EPA, 1978b)

Projected production: 12,000 metric tons (2000) (U.S. EPA, 1978b)

Since cadmium is an element, it will persist in some form in the environment. Cadmium is precipitated from solution by carbonate, hydroxide, and sulfide ions (Baes, 1973); this is dependent on pH and on cadmium concentration. Complexing of cadmium with other anions will produce soluble forms (Samuelson, 1963). Cadmium is strongly adsorbed to clays, muds, humic and organic materials and some hydrous oxides (Watson, 1973), all of which lead to precipitation from aqueous media. Cadmium corrodes slightly in air, but forms a protective surface film which prevents further corrosion (U.S. EPA, 1978b).

II. EXPOSURE

Cadmium is universally associated with zinc and appears with it in natural deposits (Hem, 1972). Major sources of cadmium release into the environment include emissions from metal refining and smelting plants, incineration of polyvinyl chloride plastics, emissions from use of fossil

Table 1. Some Properties of Cadmium and its Important Compounds

Compound	Primary use or occurrence	Formula	Molecular weight (g/mole)	Density (g/ml)	Physical state, 20°C	Melting point (°C)	Boiling point (°C)	Solubility in water 20°C (g/liter)	Solubility in other solvents	Acute lethal dose[a]
Cadmium metal	Cadmium nickel batteries	Cd	112.4	8.6	Silver metal	321	765	Insoluble	Soluble in acid and NH_4NO_3	9 mg/m^3 is the approximate lethal concentration in man, inhaled as fume
Cadmium oxide	Smelting plant or coal combustion emission	CdO	128.4	7.0	Brown powder	Decomposes at 900		0.00015[b]	Soluble in acid and NH_3 salts	50 mg/m^3 is the approximate lethal concentration in man, inhaled; 72 mg/kg, rat, LD_{50} (oral)
Cadmium sulfide	Pigment for plastics and enamels; phosphors	CdS	144.5	4.8	Yellow crystal	1750	Decomposes	0.0013	Soluble in acid, very slightly soluble in NH_4OH	
Cadmium sulfate	Fruit tree fungicide	$CdSO_4$	208.5	4.7	White crystalline	1000		755	Insoluble in acid and alcohol	37 mg/kg dog, LD_{50} (subcutaneous)
Cadmium carbonate	Turf treatment	$CdCO_3$	172.4	4.3	White powder or crystalline	Decomposes below 500		0.001	Soluble in acid and KCN, NH_4 salts	

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Table 1. Some Properties of Cadmium and its Important Compounds (Cont'd)

Compound	Primary use or occurrence	Formula	Molecular weight (g/mole)	Density (g/ml)	Physical state, 20°C	Melting point (°C)	Boiling point (°C)	Solubility in water 20°C (g/liter)	Solubility in other solvents	Acute lethal dose[a]
Cadmium chloride	Turf grass fungicide	$CdCl_2$	183.3	4.0	Colorless crystal	568	960	1400	15.2 g/liter in alcohol	88 mg/kg rat, LD_{50} (oral)
Cadmium potassium cyanide	Electroplating	$K_2Cd(CN)_4$	294.7	1.85	Colorless, glass crystal			311	Insoluble in alcohol	
Cadmium cyanide	Electroplating	$Cd(CN)_2$	164.4		Colorless crystal	Decomposes at 200		17, soluble in hot water	Soluble in acid and KCN	

Sources:

[a] Fulkerson and Goeller, 1973
[b] Helms and Brountje, 1973
Other data compiled from Weast, 1971

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fuels, use of certain phosphate fertilizers, and leaching of galvanized iron pipes (U.S. EPA, 1978b). The major non-occupational routes of human exposure to cadmium are through foods and tobacco smoke (U.S. EPA, 1979).

Based on available monitoring data, the U.S. EPA (1979) has estimated the uptake of cadmium by adult humans from air, water, and food:

Source	Adult µg/day
	Maximum conditions
Air-ambient	.008 mg/day
Air-smoking	9.0
Foods	75.0
Drinking water	20.0
Total	304.008
	Minimum conditions
Air-ambient	0.00002
Air-smoking	0
Food	12.0
Drinking water	1.0
Total	13.00002

The variation of cadmium levels in air, food, and water is quite extensive as indicated above. Leafy vegetables, contaminated water, and air near smelting plants all present sources of high potential exposure. The U.S. EPA (1979) has estimated the weighted average bioconcentration factor of cadmium to be 17 in the edible portions of fish and shellfish consumed by Americans.

III. PHARMACOKINETICS

A. Absorption

The main routes by which cadmium can enter the body are inhalation and ingestion. Particle size and solubility greatly influence the biological fate of inhaled cadmium. When a large proportion of particles are in

the respirable range, up to 25% of the inhaled amount may be absorbed (EPA, 1979). Cadmium fumes may have an absorption of up to 50%, and it is estimated that up to 50% of cadmium in cigarette smoke may be absorbed (WHO, 1977; Elinder, et al. 1976). Large particles are trapped by the mucous membranes and may eventually be swallowed, resulting in gastrointestinal absorption (EPA, 1979).

Only a small proportion of ingested cadmium is absorbed. Two human studies using radiolabelled cadmium have indicated mean cadmium absorption from the gastrointestinal tract of 6% and 4.6% (Rahola, et al. 1973; McLellan, et al. 1978). Various dietary factors interact with cadmium absorption; these include calcium levels (Washko and Cousins, 1976), vitamin D levels (Worker and Migicovsky, 1961), zinc, iron, and copper levels (Banis, et al. 1969). and ascorbic acid levels (Fox and Fry, 1970). Low protein diets enhance the uptake of cadmium from the gastrointestinal tract (Suzuki, et al. 1969).

Dermal absorption of cadmium appears to occur to a small extent; Wahlberg (1965) has determined that up to 1.8 percent of high levels of cadmium chloride were absorbed by guinea pig skin.

Cadmium levels have been determined in human embryos (Chauce, et al. 1973) and in the blood of newborns (Lauwerys, 1978), indicating passage of cadmium occurs across the placental memoranes.

B. Distribution

Cadmium is principally stored in the liver, kidneys, and pancreas with higher levels initially found in the liver (WHO Task Group, 1977). continued exposure leads to accumulation in all of these organs; levels as

high as 200-300 mg/kg wet weight may be found in the renal cortex. This storage appears to be dependent on the association of cadmium with the cadmium binding protein, metallothionen (Nordberg et al., 1975).

Animal studies indicate that following intraperitoneal or intravenous administration of cadmium most of the compound is found in the blood plasma. After 12-24 hours the plasma is cleared and most of the compound is associated with red blood cells (U.S. EPA, 1978b).

The cadmium body burden of humans increases with age (Friberg, et al. 1974) from very minimal levels at birth to an average of up to 30-40 mg by the age of 50 in non-occupationally exposed individuals. Liver accumulation continues through the last decades of life, while kidney concentrations increase until the fourth decade and then decline (Gross, et al. 1976). The pancreas and salivary glands also contain considerable concentrations of cadmium (Nordberg, 1975). Smoking effects the body burden of cadmium; levels in the renal cortex of smokers may be double those found in non-smokers (Elinder, et al. 1976; Hammer, et al. 1971).

C. Metabolism.

Pertinent data were not found in the available literature.

D. Excretion

Since only about 6 percent of ingested cadmium is absorbed, a large proportion of the compound is eliminated by the feces (U.S. EPA, a or b). Some biliary excretion of cadmium has been demonstrated in rats (Stowe, 1976); this represented less than 0.1 percent of a subcutaneously administered dose.

Urinary excretion of cadmium is approximately 1-2 mg/day in the general population (Imbus, et al. 1963; Szadkowski, et al. 1969). Occupationally exposed individuals may show markedly higher urinary excretion

levels (Friberg, et al. 1974). A modest increase in human urinary excretion of cadmium has been noted with increasing age (Katagiri, et al. 1971).

Additional sources of cadmium loss are through salivary excretion and shedding of hair (U.S. EPA, 1979).

Biological half-life calculations for exposed workers have given values of up to 200 days (urine). Direct comparisons of urinary excretion levels and estimated body burden using Japanese, American, and German data, suggest a half-time of 13-47 years. Using more complex metabolic models, Frieberg, et al. 1974 concluded that the biologic half-time is probably 10-30 years. The most recent estimate of biologic half-time is 15.7 years by Ellis (1979).

IV. EFFECTS

A. Carcinogenicity

The results of several epidemiology studies of the relationship of cancer to occupational exposure to cadmium are summarized in Table 3 (U.S. EPA, 1978a). The only consistent trend seen in these studies is an increased incidence of prostate cancer in cadmium-exposed workers. A recent study by Kjellstrom, et al. (1979) of 269 cadmium-nickel battery factory workers found increased cancer mortality from nasopharyngeal cancer (significant) and increased mortality trends for prostate, lung, and colon-rectum cancers (not significant). After reviewing these studies, EPA (1979) has concluded that cadmium cannot be definitely implicated as a human carcinogen with the available data.

Animal experiments with the administration of cadmium by subcutaneous or intravenous injection have demonstrated that cadmium produces

injection site sarcomas and testicular tumors (Leydigiomas) (see Table 2; U.S. EPA, 1978a). A large number of metals and irritants produced comparable injection site sarcomas. Long term feeding and innalation studies with cadmium have not produced tumors (Schroeder, et al. 1964, Levy, et al. 1973; Decker, et al. 1958; Anwar, et al. 1961; Paterson, 1947; Malcolm, 1972)

At the present time, the draft amoient water quality criterion for protection of human health is based on the toxicity of cadmium rather than on any carcinogenic effects. Though the studies summarized above qualitatively indicate a carcinogenic potential for cadmium, quantitatively, the issue has not been resolved.

B. Mutagenicity

An increased incidence of chromosomal aberrations has been noted in workers occupationally exposed to cadmium and in Japanese patients suffering cadmium toxicity (Itai-Itai disease) (Bauchinger, et al. 1976; Bui, et al. 1975; Deknudt and Leonard, 1976; Shiraishi and Yoshida, 1972).

Cadmium has been shown to produce mutagenic effects in vitro and in vivo in several systems (see Table 4; U.S. EPA, 1978 a or b). These effects include induction of point mutations in bacterial systems, chromosome aberrations in cultured cells and cytogenetic damage in vivo, and promotion of error prone base incorporation in DNA in vitro. Several investigators have been unable to show dominant lethal effects of cadmium in mice (Epstein, et al. 1972; Gillivod and Leonard, 1975; Suter, 1975). Point mutation studies with cadmium in Drosophila have also produced negative findings (Shabalina, 1968; Friberg et al., 1974; Sorsa and Pfeiffer, 1973).

C. Teratogenicity

Damage to the reproductive tract resulting from a single dose of parenterally administered cadmium chloride (2 mg/kg) have been observed in

TABLE 2

STUDIES ON CADMIUM CARCINOGENESIS IN EXPERIMENTAL ANIMALS[a]

Authors	Animals	Compounds and routes	Tumors
Heath et al., 1962; Heath and Daniel, 1964	Rats	Cd powder in fowl serum (im)[b]	Sarcomas
Kazantzis, 1963; Kazantzis and Henbury, 1966	Rats	CdS, Cdo (sc)[b]	Sarcomas
Haddow et al., 1964; Roe et al., 1964	Rats	$CdSO_4$, $CdCl_2$ (sc)	Sarcoma and Leydigiomas
Guthrie, 1964	Chickens	$CdCl_2$ (intratesticular)	Teratoma
Gunn et al., 1963; 1964; 1965; 1967	Rats, Mice	$CdCl_2$ (im)	Sarcomas and Leydigiomas
Schroeder et al., 1965; Kanisawa and Schroeder, 1969	Rats, Mice	Cd-acetate (drinking water)	No Tumorigenic Effect
Nazari et al., 1967; Favion et al., 1968	Rats	$CdCl_2$ (sc)	Sarcomas and Leydigiomas
Knorre, 1970; 1971	Rats	$CdCl_2$ (sc)	Sarcomas and Leydigiomas
Lucis et al., 1972; 1973	Rats	$CdCl_2$ (sc, intrahepatic)	Sarcomas and Leydigiomas
Reddy et al., 1973	Rats	$CdCl_2$ (sc)	Leydigiomas
Levy et al., 1973	Rats	$CdSO_4$ (sc)	Sarcomas
Levy and Clark, 1975; Levy et al., 1975	Rats, Mice	$CdSO_4$ (gastric intubation)	No Tumorigenic Effect

[a]Adapted from Sunderman, 1977.

[b]Intramuscular: im; subcutaneous: sc.

TABLE 3

SUMMARY OF RESULTS OF HUMAN EPIDEMIOLOGY STUDIES OF CANCER EFFECTS ASSOCIATED WITH OCCUPATIONAL EXPOSURES TO CADMIUM

Population Group Studied	Cadmium Compound Exposed To	Incidences of All Cancers	Incidences of Lung Cancer	Incidences of Prostrate Cancer	Reference
Battery factory workers	Cadmium oxide	High	Normal	High	Potts (1965)
Battery factory workers	Cadmium oxide	Normal	Normal	High	Kipling and Waterhouse (1967)
Cadmium smelter workers	Cadmium oxide, others	High	High	High	Lemon et al. (1976)
Rubber industry workers	Cadmium oxide	High	Normal	High	McMichael et al. (1976)

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rats, rabbits, guinea pigs, hamsters, and mice (Parizek and Zahor, 1956; Parizek, 1957; Meek, 1959). This susceptibility appears to be genetically regulated since different strains of mice show differential susceptibility (Wolkowski, 1975).

Teratogenic effects of cadmium compounds administered parenterally have been reported in mice (Eto, et al. 1975), hamsters (Ferm and Carpenter, 1968; Mulvihill, et al. 1970; Ferm, 1971; Gale and Ferm, 1973) and rats (Chernoff, 1973; Barr, 1973). Oral administration of cadmium (10 ppm) has demonstrated teratogenic effects in rats (Schroeder and Mitchener, 1971), but no teratogenicity has been reported in rats and monkeys (Cuetkova, 1970; Pond and Walker, 1975; Willis, et al. 1976; Campbell and Mills, 1974).

D. Other Reproductive Effects

Rats in late pregnancy are apparently more sensitive to cadmium than non-gravid animals or those immediately post-partum. A single dose of 2-3 mg/kg of body weight given during the last 4 days of pregnancy resulted in high mortality (76 percent).

In addition to the embryotoxic effects of cadmium indicated in Section C, persisting effects of cadmium exposure during pregnancy on postulated development and growth of offspring have been observed. This includes neurobehavioral alteration in newborn rats (Chowdbury and Lauria, 1976) and growth deficiencies in lambs (U.S. EPA, 1978a).

E. Chronic Toxicity

Friberg (1948, 1950) observed emphysema in workmen exposed to cadmium dust in an alkaline battery factory. This finding has subsequently been well documented (U.S. EPA, 1979).

TABLE 4

SUMMARY OF MUTAGENICITY TEST RESULTS

Test System	Genetic Effect	Reported Mutagenicity	References
	Systems in vitro		
Human cells	Chromosomal damage	+	Shiraishi et al., 1972
Chinese Hamster Cells	Point mutation	+	Costa et al., 1976
S. cerevisiae	Point mutation	+	Takahoshi, 1972
B. subtilis recombinant assay	Gene mutation	+	Nishioka, 1975
Polynucleotides	Base mispairing	+	Sirover and Loeb, 1976
	Systems in vivo		
Human leukocytes	Chromosomal damage	+	Shirashi and Yoshida, 1972
Human leukocytes	Chromosomal damage	-	Bui et al., 1975
Human leukocytes	Chromosomal damage	+	Deknudt and Leonard, 1975
Human leukocytes	Chromosomal damage	+	Bauchinger et al., 1976
Rat spermatogonia	Altered spermatogenesis	+	Lee and Dixon, 1973
Mouse oocytes	Cytogenetic damage	+	Shimada et al., 1976
Mouse breeding	Dominant lethal mutations	-	Epstein et al., 1972
Mouse breeding	Dominant lethal mutations	-	Gilliavod and Leonard, 1975
Mouse breeding	Dominant lethal mutations	-	Suter, 1975
Mammals	Chromosomal abnormalities	-	Shimada et al., 1976
D. melanogaster	Sex-linked recessive lethal	-	Sorsa and Pfeifer, 1973

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Chronic cadmium exposure produces renal tabular damage that is characterized by the appearance of a characteristic protein (β_2-microglobulin) in the urine. Renal damage has been estimated to occur when cadmium levels in the renal cortex reach 200 mg/kg (Kjellstron, 1977). Itai-Itai disease is the result of cadmium induced renal damage plus osteomalacia (U.S. EPA, 1978a).

Exposure to high ambient cadmium levels may contribute to the etiology of hypertension (U.S. EPA, 1979). Several studies, however, have been unable to show a correlation between renal levels of cadmium and hypertension (Morgan 1972; Lewis, et al. 1972; Beevers, et al. 1976).

Friberg (1950) and Blejer (1971) have noted abnormal liver function tests in workers exposed to cadmium; however, these workers were occupationally exposed to a variety of agents.

The immunosuppressive effects of cadmium exposure, including an increased susceptibility to various infections, have been reported in several animal studies (Cook, et al! 1975; Koller, 1973; Exon, et al. 1975).

V. AQUATIC TOXICITY

A. Acute Toxicity

Acute toxicity in freshwater fish has been studied in a number of 96-hour bioassays consisting of one static renewal, 22 static, and 19 flow-through tests. LC_{50} values ranged from 1 µg/l for striped bass larvae (Roccus saxatilus) (Hughes, 1973) to 73,500 for the fathead minnow (Pimephales promelas) (Pickering and Henderson, 1966). Increased resistance to the toxic action of cadmium in hard waters was observed. The LC_{50} values for freshwater invertebrates ranged from 3.5 for Cladoceran (Simoecphalus serrulatus) to 28,000 µg/l for the mayfly (Ephemerella grandis grandis). Acute LC_{50} values for marine fish ranged from 1,600 µg/l for

larval Atlantic silversides (Menidia menida) (Middaugh and Dean, 1977) to 114,000 µg/l for juvenile mummichog (Fundulus heteroclitus) (Voyer, 1975). Intraspecific and life stage differences have shown that larval stages of the Atlantic silversides and mummichog are four times more sensitive than adults under the same test conditions (Middaugh and Dean, 1977). Marine invertebrates are more sensitive to cadmium than are marine fishes. LC_{50} values ranged from 15.5 µg/l for the mysid shrimp (Nimmo, et al. 1977a) to 46,600 for the fiddler crab (Uca pugilator) (O'Hara, 1973).

B. Chronic Toxicity

Chronic values for freshwater fish ranged from 0.9 µg/l in a brook trout (Salvelinus fontinalis) embryo larval assay (Sauter, et al. 1976) to 50 µg/l in a life cycle (or partial life cycle) assay for the bluegill (Lepomis marcochirus) in hard water (Eaton, 1974). Salmonids were in general the most sensitive species examined. Data for freshwater invertebrates depend on a single µg/l obtained for Daphnia magna (Biesinger and Christensen, 1972). No chronic studies were available for cadmium effects in marine fishes. The only marine invertebrates data reported was the chronic value of 5.5 µg/l for the mysid shrimp, Mysidopsis bahia. In this animal no measurable effects on brood appearance in the pouch, release, average number per female, or survival were observed at concentrations of 4.8 µg/l.

C. Plant Effects

Effective concentrations for freshwater plants ranged from 2 µg/l, which causes a 10 fold growth rate decrease in the diatom, Asterionella formosa (Conway, 1978), to 7,400 µg/l, which causes a 50% root weight inhibition in Eurasian water-milfoil (Myriophyllum spicatum). In marine algae,

96-hour EC_{50} growth rate assays yielded values of 160 and 175 µg/l for Cyclotella nana and Skeletonema costatum respectively (Gentile and Johnson, 1974).

D. Residues

Bioconcentration factors ranged from 151 for brook trout to 1,988 for the flagfish (Jordanella floridae). One characteristic of cadmium toxicity in aquatic organisms was the possible long half-life of the chemical in certain tissues of exposed brook trout even after being placed in clean water for several weeks. Testicular damage to adult mallards was observed when fed 20 mg/kg cadmium in the diet for 90 days. In marine organisms bioconcentration values ranged from 37 for the shrimp Crangon crangon to 1,230 for the American oyster, Crassostrea virginica (Schuster and Pringle, 1969).

E. Miscellaneous

Several studies on marine organisms have demonstrated significant reduction in gill-tissues respiratory rates in the cunner, Tautogolabrus adspersus, the winter flounder, Pseudopleuronectes americanus, and the striped bass, Morone saxatilis, at concentrations as low as 0.5 µg/l.

VI. EXISTING GUIDELINES

A. Human

It is not recommended that cadmium be considered a suspect human carcinogen for purposes of calculating a water quality criterion (U.S. EPA, 1979).

The EPA Primary Drinking Water Standard for protection of human health is 10 µg/l. This level was also adopted as the draft ambient water quality criterion (U.S. EPA, 1979).

The OSHA time-weighted average exposure criterion for cadmium is 100 $\mu g/m^3$.

B. Aquatic

The draft criterion proposed for freshwater organisms to cadmium has been prepared following the Guidelines, and is listed according to the following equation:

$$e^{(0.867\ \ln(\text{hardness}) - 4.38)}$$

for a 24-hour average and not to exceed the level described by the following equation:

$$e^{(1.30\ \ln(\text{hardness}) - 3.92)}$$

The proposed marine criterion derived following the Guidelines is 1.0 µg as a 24-hour average not to exceed 16 µg/l at any time (U.S. EPA, 1979).

CADMIUM

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LB:44-1

No. 32

Carbon Disulfide

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OCTOBER 30, 1980

CARBON DISULFIDE

I. PHYSICAL AND CHEMICAL PROPERTIES

CS_2 (FW 76.14) is soluble in water at 0.294% (20°C), and chelates trace metals, especially Cu and Zn. It is a colorless, volatile, and extremely flammable liquid at RT. CS_2 has no odor when pure.

II. PRODUCTION AND USE

CS_2 is produced in petroleum and coal tar refining. Its principal uses are as a solvent in the manufacture of rayon, rubber, chemicals, solvents, and pesticides.[1] In 1974, 782 million pounds of CS_2 were produced in the United States.[2] In 1971, 53% was used in production of viscose rayon and cellphane and 25% for manufacture of CC_{14}.

III. EXPOSURE

CS_2 was detected in 5 of 10 water supplies surveyed by the EPA.[3] NIOSH[25] estimates that in the U.S. 20,000 employees are potentially exposed to CS_2.

III. PHARMACOKINETICS

A. Absorption: Absorption differs with species and route of administration[4]; inhalation and skin absorption are the most important routes for humans (31).

B. Distribution: Large concentrations of both free and bound CS_2 are found in brain (guinea pig) and peripheral nerves (rats) of exposed animals. The ratio of bound to

free CS_2 is brain 3:1. Blood and fatty tissues contain mainly bound CS_2, while liver contains CS_2 mainly in the free (unbound) form.[4]

C. Metabolism: CS_2 is 90% metabolized by the P-450 system to inorganic sulfate.[5] A portion of the S released by CS_2 is thought to react with SH groups of cysteine residues in the microsomal proteins to form hydro-sulfide.[6]

D. Excretion: small amounts of CS_2 metabolites such as thiourea, 5-mercaptothioazolidone, and inorganic constituents are excreted in urine.[7] Inhalation studies have shown that 18% of the CS_2 inhaled is exhaled unchanged. Of the remaining inhaled dose, 70% is excreted as free or bound CS_2 and urinary sulfates, and 30% is stored in the body and slowly excreted as CS_2 and its metabolites.

V. EFFECTS ON MAMMALS

A. Carcinogenicity: No available data.[4]

B. Mutagenicity: No available data.[4]

C. Teratogenicity: Bariliah et al.[8] showed that inhalation of 10 mg/m^3 is lethal to embryos before and after implantation. CS_2 at 2.2 mg/m^3 inhaled for 4 hours/day was toxic to dams, and embryotoxic if administered during gestation, and had no effect on male rats.[9] Inhalation of lower concentrations (0.34 mg/l for 210 days) caused disturbances of estrus.[10] Topical application of CS_2 induced teratogenic effects in rats.[3] In a dominant lethal test, inhalation of 10 mg/m^3 by male rats before copulation proved lethal to embryos.[8]

D. Toxicity

1. Humans

CS_2 causes damage to the central and peripheral nervous systems and may accelerate the development of, or worsen, coronary heart disease.[31]

The lowest lethal concentration has been reported as 4,000 ppm in 30 minutes.[11] In the same study, a person subjected to a concentration of 50 mg/m^3 for 7 years had CNS effects. Moderate chronic exposure of humans at less than 65 mg/m^3 for several years has been reported by Cooper[12] to cause polyneuropathy. In a study by Baranowska et al.[13] humans have been shown to absorb 8.8-37.2 mg from an aqueous solution containing 0.33-1.67 gm/l. This was over a period of 1 hour of hand-soaking.

In poisoning due to continued exposure at fairly low levels (0.9-378 ppm)[31] neuritis and visual disturbances are the most common symptoms.[31,32] Sensory changes, sensations of heaviness and coldness, "veiling" of objects, pain in affected limbs, are often followed by gradually increasing loss of strength. Mental symptoms varying in severity (excitation, irritability, personality changes, insomnia, and even insanity) may occur.[32]

There are several studies on cardiovascular effects of CS_2 exposure.[26-29] Heinberg et al.[26,27] report significantly elevated rates of coronary heart disease mortality, angina, and high blood pressure in viscose rayon workers. A five year follow-up again reported increased

coronary heart disease mortality and higher than expected incidences of total infarctions, nonfatal infarctions and angina. In an 8-year followup in 1976, Heinberg[30] found no excess coronary heart disease mortality during the last 3 years of the study.

2. Other species.

IP injection of 400 mg/kg was the lowest lethal dose in guinea pigs.[14] An IV LD50 of 694 mg/kg in mice was reported by Hylen and Chin.[15]

Toxic effects have been observed at doses as low as 1.7 mg/kg in rabbits.[17] Rats showed toxic SC effects at 1 mg/kg.[17-19] Vinogradov[20] showed that 1 ppm in drinking water was nontoxic to rabbits; 70 ppm was fatal.

In a chronic study, Paterni et al.[21] found that 6 mg/kg/day produced toxic effects in rabbits. The lowest lethal chronic dose for rabbits was shown to be 0.1 ml 3 times a week for 7 months.[22] Applied topically, CS_2 produced higher incidence of

anemia in female than in male rats, and teratogenic effects (see above) were observed.[23] When rats inhaled CS_2 at 10 mg/m^3, abnormalities of genitourinary and skeletal systems were noted. In addition, disturbances of ossification and blood formation and dystrophic changes in liver and kidney were noted.[8]

VI. EXISTING GUIDELINES AND STANDARDS

The NAS[4] did not recommend limits for drinking water

because estimates of effects of chronic oral exposure cannot be made with any confidence.

The current OSHA PEL is 20 ppm (62 mg/m^3), with a ceiling concentration of 30 ppm (93 mg/m^3) for an 8-hour day, 5 day work week.[25] The NIOSH[24] recommended standard is 3 mg/m^3.[24]

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No. 33

Carbon Tetrachloride (Tetrachloromethane)

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

~~-374~~

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated carbon tetrachloride and has found sufficient evidence to indicate that this compound is carcinogenic.

CARBON TETRACHLORIDE

Summary

Carbon tetrachloride (CCl_4) is a haloalkane with a wide range of industrial and chemical applications. Toxicological data for non-human mammals are extensive and show that CCl_4 causes liver and kidney damage, biochemical changes in liver function, and neurological damage. CCl_4 has been found to induce liver cancer in rats and mice. Mutagenic effects have not been observed and teratogenic effects have not been conclusively demonstrated.

The data base on aquatic toxicity is limited. LC_{50} (96-hour) values for bluegill range from 27,300 tc 125,000 µg/l in static tests. For Daphnia magna, the reported 48-hour EC_{50} is 35,200 µg/l. The 96-hour LC_{50} for the tidewater silverside is 150,000 µg/l. An embryo-larval test with the fathead minnow showed no adverse effect from carbon tetrachloride concentrations up to 3,400 µg/l. No plant effect data are available. The bluegill bioconcentrated carbon tetrachloride to a factor of 30 times within 21 days expcsure. The biological half-life in the bluegill was less than 1 day.

CARBON TETRACHLORIDE

I. INTRODUCTION

Carbon tetrachloride (CCl_4) is a haloalkane with a wide range of industrial and chemical applications. Approximately 932.7 million pounds are produced at 11 plant sites in the U.S. (U.S. EPA, 1977b; Johns, 1976). The bulk of CCl_4 is used in the manufacture of fluorocarbons for aerosol propellants. Other uses include grain fumigation, a component in fire extinguisher solutions, chemical solvent, and a degreaser in the dry cleaning industry (Johns, 1976).

Carbon tetrachloride is a heavy, colorless liquid at room temperature. Its physical/chemical properties include: molecular weight, 153.82; melting point, -22.99°C; solubility in water, 800,000 µg/l at 25°C; and vapor pressure, 55.65 mm Hg at 10°C. CCl_4 is relatively non-polar and miscible with alcohol, acetone and most organic solvents.

Carbon tetrachloride may be quite stable under certain environmental conditions. The hydrolytic breakdown of CCl_4 in water is estimated to require 70,000 years for 50 percent decomposition (Johns, 1976). This decomposition is accelerated in the presence of metals such as iron (Pearson and McConnell, 1975). Hydrolytic decomposition as a means of removal from water is insignificant when compared with evaporation. In one experiment the evaporative half-life of CCl_4 in water at ambient temperatures was found to be 29 minutes (Dilling, et al. 1975), but this is highly dependent on experimental conditions, such as surface area to bulk volume ratios. For additional information regarding Halomethanes as a class, the reader is referred to the Hazard Profile on Halomethanes (U.S. EPA, 1979b).

II. EXPOSURE

A. Water

CCl_4 has been found in many water samples including rain, surface, potable, and sea, in the sub-part per billion range (McConnell, et al. 1975). The National Organics Monitoring Survey (NOMS) found CCl_4 in 10 percent of 113 public water systems sampled, with mean values ranging from 2.4-6.4 µg/l (U.S. EPA, 1977a).

Although CCl_4 is a chlorinated hydrocarbon, it is not produced in finished drinking water as a result of the chlorination process (Natl. Res. Coun., 1977,1978).

B. Food

Carbon tetrachloride has been detected in a variety of foodstuffs other than fish and shellfish in levels ranging from 1 to 20 µg/kg (McConnell, et al. 1975).

Results of various studies on CCl_4 fumigant residues in food indicate that the amount of residue is dependent upon fumigant dosage, storage conditions, length of aeration and the extent of processing (U.S. EPA, 1979a). Usually, proper storage and aeration reduce CCl_4 residues to trace amounts.

The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor for carbon tetrachloride to be 69 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on measured steady-state bioconcentration studies in bluegills.

C. Inhalation

The occurrence of CCl_4 in the atmosphere is due largely to the volatile nature of the compound. Concentrations of CCl_4 in continental and marine air masses range from .00078 - .00091 mg/m^3. Although some

higher quantities (.0091 mg/m^3) have been measured in urban areas, concentrations of CCl_4 are universally widespread with little geographic variation (U.S. EPA, 1979a).

III. PHARMACOKINETICS

A. Absorption

CCl_4 is readily absorbed through the lungs, and more slowly through the gastrointestinal tract (Nielsen and Larsen, 1965). It can also be absorbed through the skin. The rate and amount of absorption are enhanced with the ingestion of fat and alcohol (Nielson and Larson, 1965; Moon, 1950). Robbins (1929) found that considerable amounts of CCl_4 are absorbed from the small intestine, less from the colon, and little from the stomach. Absorption from the gastorintestinal tract appears to vary by species, i.e., it occurs more rapidly in rabbits than dogs.

B. Distribution

The organ distribution of CCl_4 varies with the route of administration, its concentration, and the duration of exposure (U.S. EPA, 1979a).

After oral administration to dogs, Robbins (1929) found the highest concentrations of CCl_4 in the bone marrow. The liver, pancreas and spleen had one-fifth the amount found in the bone marrow. The highest concentrations of CCl_4 after inhalation, however, were found in the brain (Von Oettingen, et al. 1949,1950). After inhalation of CCl_4 by monkeys, the highest levels were detected in fat, followed by liver and bone marrow (McCollister, et al. 1950). McConnell, et al. (1975) found human tissue levels of CCl_4 to range as follows: kidney, 1-3 mg/l; liver, 1-5 mg/l and fat, 1-13 mg/l.

On the cellular level, McClean, et al. (1965) found CCl_4 in all cell fractions with higher concentrations in ribosomes.

C. Metabolism

When CCl_4 is administered to mammals, it is metabolized to a small extent, the majority being excreted through the lungs. The metabolites include chloroform, hexachloroethane, and carbon dioxide. These metabolites play an important role in the overall toxicity of CCl_4 (U.S. EPA, 1979a). Some of the CCl_4 metabolic products are also incorporated into fatty acids by the liver and into liver microsomal proteins and lipids (Gordis, 1969).

The chemical pathology of liver injury induced by CCl_4 is a result of the initial homolytic cleavage of the C-Cl bond which liberates trichloromethyl- and chlorine-free radicals (Fishbein, 1976). The next step may be one of two conflicting reactions: direct attack via alkylation on cellular constituents (especially sulfhydryl groups), or peroxidative decomposition of lipids of the endoplasmic reticulum as a key link between the initial bond cleavage and the pathological phenomena characteristic of CCl_4 (Butler, 1961; Tracey and Sherlock, 1968).

D. Excretion

The largest portion of absorbed CCl_4 is rapidly excreted. Approximately 50-79 percent of absorbed radioactive CCl_4 is eliminated through the lungs, and the remainder is excreted in the urine and feces. No CCl_4 was detected in the blood or in the expired air, 48 hours and 6 days, respectively, after CCl_4 inhalation (Beamer, et al. 1950). CCl_4 is excreted as 85 percent parent compound, 10 percent carbon dioxide, and smaller quantities of other products including chloroform (NRC, 1977).

IV. EFFECTS

A. Carcinogenicity

CCl_4 has been shown to be carcinogenic in rats, mice, and hamsters via subcutaneous injection, intubation, and rectal instillation (U.S.

EPA, 1979). Current knowledge lead to the conclusion that carcinogenesis is a non-threshold, non-reversible process. However, some scientists do argue that a threshold may occur.

Rueber and Glover (1970) administered injections of 1.3 ml/kg of body weight of a 50 percent solution of CCl_4 in corn oil to rats, two times per week until death. Carcinoma of the liver were present in 12/15 (80 percent) Japanese male rats, 4/12 (33 percent) Wistar rats, and 8/13 (62 percent) Osborne-Mendel rats, whereas Black Rats or Sprague-Dawley rats did not develop carcinomas. The incidence of cirrhosis of the liver also differed with the strain of the rat. Carcinoma of the liver tended to develop along with mild or moderate, rather than severe cirrhosis of the liver. When administered with CCl_4, methylcholanthrene (a potent enzyme inducer) was found to increase the incidence of hyperplastic hepatic nodules and early carcinomas in rats (Rueber, 1970). Females were found to be more susceptible to the development of hyperplastic nodules and carcinomas.

The National Cancer Institute (1976) studied the carcinogenic effect of CCl_4 in male and female mice (1,250 mg/kg or 2,500 mg/kg of body weight, oral gavage 5 times/week/78 weeks). Hepatocellular carcinomas were found in almost all of the mice receiving CCl_4. Andervant and Dunn (1955) transplanted 30 CCl_4-induced tumors into mice. They observed growth in 28 of the hepatomas, through 4 to 6 transplant generations.

B. Mutagenicity

Conclusive evidence on the mutageniciity of CCl_4 has not been reported. Kraemer, et al. (1976) found negative results using the Ames bacterial reversion tests. However, they explain that halogenated hydrocarbons are usually negative in the Ames test.

C. Teratogenicity

Very little data are available concerning the teratogenic effects of CCl_4. Schwetz, et al. (1974) found CCl_4 to be slightly embryotoxic, and to a certain degree retarded fetal development, when administered to rats at 300 or 1,000 mg/l for 7 hr/day on days 6 through 15 of gestation. Bhattacharyya (1965) found that subcutaneous injection occasionally gave rise to changes in fetal liver.

D. Other Reproductive Effects

Pertinent data concerning other reproductive effects of CCl_4 were not encountered in the available literature.

E. Chronic Toxicity

Cases of chronic poisoning have been reported by Butsch (1932), Wirtschafter (1933), Strauss (1954), Von Oettingen (1964), and others. The clinical picture of chronic CCl_4 poisoning is much less characteristic than that of acute poisoning. Von Oettingen (1964) has done an excellent job of reviewing the symptoms. Patients suffering from this condition may complain of fatigue, lassitude, giddiness, anxiety, and headache. They suffer from paresthesias and muscular twitchings, and show increased reflex excitability. They may be moderately jaundiced, have a tendency to hypoglycemia, and biopsy specimens of the liver may show fatty infiltration. Patients may complain of a lack of appetite, nausea, and occasionally of diarrhea. In some instances, the blood pressure is lowered and is accompanied by pain in the cardiac region and mild anemia. Other patients have developed pain in the kidney region, dysuria, and slight nocturia, and have had urine containing small amounts of albumin and a few red blood cells. Burning of the eyes and, in a few instances, blurred vision are frequent complaints of those exposed. If these symptoms are not pronounced, or of long

standing, recovery usually takes place upon discontinuation of the exposure if the proper treatment is received (Von Oettingen, 1964).

Reports on pathological changes in fatalities from CCl_4 poisonings are generally limited to findings in the liver and kidneys. The brain and lungs may be edematous. The intestines may be hyperemic and covered with numerous petechial hemorrhages and the spleen may be enlarged and hyperemic. Occasionally the adrenal glands may show degenerative changes of the cortex and the heart may undergo toxic myocarditis (Von Oettingen, 1964).

F. Other Relevant Information

The toxic effects of CCl_4 are potentiated by both the habitual and occasional ingestion of alcohol (U.S. EPA, 1979a). Pretreatment of laboratory animals with ethanol, methanol, or isopropanol increases the susceptibility of the liver to CCl_4 (Wei, et al. 1971; Traiger and Plaa, 1971).

Hafeman and Hoekstra (1977) reported that protective effects against CCl_4-induced lipid peroxidation are exhibited by vitamin E, selenium, and methionine.

According to Davis (1934), very obese or undernourished persons or those suffering from pulmonary diseases, gastric ulcers or a tendency to vomiting, liver or kidney diseases, diabetes or glandular disturbances, are especially sensitive to the toxic effect of CCl_4 (Von Oettingen, 1964).

V. AQUATIC TOXICITY

A. Acute Toxicity

Two studies have investigated the acute toxicity of carbon tetrachloride to bluegills (Lepomis macrochirus) in static tests. The determined LC_{50} varied from 27,300 µg/l to 125,000 µg/l (Dawson, et al. 1977; U.S. EPA, 1978). With Daphnia magna, the reported 48-hr. EC_{50} is 35,200 µg/l (U.S. EPA, 1978). The 96-hr. LC_{50} for the tidewater silversides (Menidia beryllina) is 150,000 µg/l (Dawson, et al. 1977).

B. Chronic Toxicity

An embryo-larval test with the fathead minnow (Pimephales promelas) showed no adverse effect from carbon tetrachloride concentrations up to 3,400 µg/l (U.S. EPA, 1978). Other chronic data are not available.

C. Plant Effects

There are no data in the available literature describing the effects of carbon tetrachloride on freshwater or saltwater plants.

D. Residues

The bluegill bioconcentrated carbon tetrachloride to a factor of 30 times within 21 days. The biological half-life in these tissues was less than 1 day.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have been reviewed; therefore, there is a possibility that these criteria will be changed.

A. Human

The American Conference of Governmental Industrial Hygienists (1971) recommends a threshold limit value (TLV) of 10 mg/m^3 for CCl_4, with peak values not to exceed 25 mg/m^3 even for short periods of time. The Occupational Safety and Health Administration adopted the American National Standards Institute (ANSI, 1967) standard Z37.17 - 1967 as the Federal standard for CCl_4 (29 CFR 1910.1000). This standard is 10 mg/m^3 for an 8-hour TWA, with an acceptable ceiling of 25 mg/m^3 and a maximum peak for 5 minutes in any 4-hour period of 200 mg/m^3.

The draft ambient water quality criteria for carbon tetrachloride has been set to reduce the human carcinogenic risk levels to 10^{-5}, 10^{-6} or 10^{-7} (U.S. EPA, 1979a). The corresponding criteria are 2.6 µg/l, 0.26

µg/l, and 0.026 µg/l, respectively. Refer to the Halomethane Hazard Profile for discussion of criteria derivation (U.S. EPA, 1979b).

8. Aquatic

For carbon tetrachloride, the drafted criteria to protect freshwater aquatic life is 620 µg/l as a 24-hour average and the concentration should never exceed 1,400 µg/l at any time. To protect saltwater aquatic life, the drafted criterion is 2,000 µg/l as 24-hour average and the concentration should not exceed 4,600 µg/l at any time (U.S. EPA, 1979a).

No. 34

Chloral

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

CHLORAL

Summary

Chloral (trichloroacetaldehyde) is used as an intermediate in the manufacture of DDT, methoxychlor, DDVP, naled, trichlorfon, and TCA. Chloral is readily soluble in water, forming chloral hydrate. Chloral hydrate decomposes to chloroform with a half-life of two days. Chloral hydrate has been used as a therapeutic agent due to its hypnotic and sedative properties.

Chloral (as chloral hydrate) has been identified in chlorinated water samples at concentrations as high as 5.0 µg/l. Chloral hydrate is formed through the chlorination of natural humic substances in the raw water. Atmospheric chloral concentrations up to 273.5 mg/m^3 have been reported from spraying and pouring of polyurethanes in Soviet factories. Similar data on exposure levels in U.S. plants were not found in the available literature.

Specific information on the pharmacokinetic behavior, carcinogenicity, mutagenicity, teratogenicity, and other reproductive effects of chloral was not found in the available literature. However, the pharmacokinetic behavior of chloral may be similar to chloral hydrate where metabolism to trichloroethanol and trichloroacetic acid and excretion via the urine (and possibly bile) have been observed. Chloral hydrate produced skin tumors in 4 of 20 mice dermally exposed. Information on the chronic or acute effects of chloral in humans was not found in the available literature. Chronic effects from respiratory exposure to chloral as indicated in laboratory animals include reduction of kidney function and serum transaminase activity, change in central nervous system function (unspecified), decrease in

antitoxic and enzyme-synthesizing function of the liver, and alteration of morphological characteristics of peripheral blood. Slowed growth rate, leukocytosis and changes in arterial blood pressure were also observed. Acute oral LD_{50} values in rats ranged from 0.05 to 1.34 g/kg.

U.S. standards and guidelines for chloral were not found in the available literature.

CHLORAL

ENVIRONMENTAL FATE

Chloral (trichloroacetaldehyde) is freely soluble in water, forming chloral hydrate (Windholz, et al. 1976). Chloral hydrate was identified in drinking water from 6 of 10 cities sampled (Keith, 1976). The author postulated that chloral hydrate was formed by the chlorination of other compounds during the addition of chlorine to the water supplies. Chloral hydrate was not identified prior to chlorination. Chloral hydrate may be formed by the chlorination of ethanol or acetaldehyde and may occur as an intermediate in the reaction involving the conversion of ethanol to chloroform as follows:

Ethanol - Acetaldehyde - Chloral - Chloral hydrate - Chloroform

Chloral hydrate decomposes to chloroform with a half-life of 2 days at pH 8 and 35°C (Luknitskii, 1975). Rook (1974) demonstrated the formation of haloforms from the chlorination of natural humic substances in raw water.

Chloral polymerizes under the influence of light and in the presence of sulfuric acid, forming a white solid trimer called metachloral (Windholz, 1976). Dilling, et al. (1976) studied the effects of chloral on the decomposition rates of trichloroethylene, NO, and NO_2 in the atmosphere and observed that chloral increases the photodecomposition rate of trichloroethylene to a greater extent than it does NO or NO_2.

CHLORAL

I. INTRODUCTION

This profile is based on literature searches in Biological Abstracts, Chemical Abstracts, MEDLINE, and TOXLINE.

Chloral [Cl_3CCHO], also referred to as trichloroacetaldehyde, anhydrous chloral, and trichloroethanol, is an oily liquid with a pungent, irritating odor. The physical properties of chloral are: molecular weight, 147.39; melting point, -57.5°C; boiling point, 97.75°C at 760 mm Hg; density, 1.5121 at 20/4°C (Weast, 1976). The compound is very soluble in water, forming chloral hydrate, and is soluble in alcohol and ether.

Industrial production of chloral involves direct chlorination of ethyl alcohol followed by treatment with concentrated sulfuric acid (Stanford Research Institute, 1976). Production may also occur by direct chlorination of either acetaldehyde or paraldehyde in the presence of antimony chloride. Prior to 1972, essentially all chloral produced was used in the manufacture of DDT. Production of chloral was greatest in 1963 at 79.8 million pounds, decreasing to 62.4 million pounds in 1969. Production data after 1969 were not reported. Consumption of chloral for DDT manufacture was estimated at 25 million pounds in 1975, with an additional 500,000 pounds used in the manufacture of other pesticides, including methoxychlor, DDVP, naled, trichlorfon, and TCA (trichloroacetic acid). Mel'nikov, et al. (1975) identified chloral as an impurity in chlorofos.

Chloral is also used in the production of chloral hydrate, a therapeutic agent with hypnotic and sedative effects used prior to the introduction of barbituates. Production of U.S.P. (pharmaceutical) grade chloral hydrate was estimated to be 300,000 pounds per year in 1975 (Stanford Research Institute, 1976).

II. EXPOSURE

Boitsov, et al. (1970) noted that chloral is evolved in spraying and pouring of polyurethane. The authors reported chloral concentrations as high as 273.5 mg/m^3 in Soviet factories. Similar information on atmospheric occupational exposure to chloral in Western countries was not found in the available literature.

Chloral exposure from water occurs as chloral hydrate. Keith (1976) reported chloral hydrate concentrations ranging from 0.01 µg/l to 5.0 µg/l in chlorinated drinking water supplies of six of ten U.S. cities studied. The mean concentration of chloral hydrate in drinking water for the six cities was 1.92 µg/l.

Chloral hydrate has been used as a hypnotic and sedative agent. Alcohol synergistically increases the depressant effect of the compound, creating a potent depressant commonly referred to as "Mickey Finn" or "knockout drops". Addiction to chloral hydrate through intentional abuse of the compound has been reported (Goodman and Gilman, 1970).

III. PHARMACOKINETICS

A. Absorption

Specific information on the absorption of chloral was not found in the available literature. Goodman and Gilman (1970) reported that chloral hydrate readily penetrates diffusion barriers in the body.

B. Distribution

Specific information on the distribution of chloral was not found in the available literature. Goodman and Gilman (1970), reporting on the distribution of chloral hydrate from oral administration, noted its presence in cerebrospinal fluid, milk, amniotic fluid, and fetal blood. The authors

noted that other investigators were unable to detect significant amounts of chloral hydrate in the blood after oral administration (owing probably to its rapid reduction).

C. Metabolism

Information on the metabolic reaction of chloral is obtained indirectly through a metabolic study of trichloroethylene (Henschler, 1977). The author reported that trichloroethylene oxidizes to a chlorinated epoxide which undergoes molecular rearrangement to chloral, which is further metabolized to either trichloroethanol or trichloroacetic acid. The rearrangement, detected by in vivo studies, is hypothesized to occur by a catalytic action of the trivalent iron of P-450.

Goodman and Gilman (1970) noted that chloral hydrate is reduced to trichloroethanol in the liver and other tissues, including whole blood, with the reaction catalyzed by alcohol dehydrogenase. Additional trichloroethanol is converted to trichloroacetic acid. Chloral hydrate may be directly oxidized to trichloroacetic acid in the liver and kidney.

D. Excretion

Both chloral and chloral hydrate are metabolized to trichloroethanol or trichloroacetic acid (Goodman and Gilman, 1970; Henschler, 1977). Trichloroethanol is then conjugated and excreted in the urine as a glucuronide (urochloralic acid) or is converted to trichloroacetic acid and slowly excreted in the urine. The glucuronide may also be concentrated and excreted in the bile. The fraction of the total dose excreted as trichloroethanol, glucuronide, and trichloroacetic acid is quite variable, indicating other possible routes of elimination.

IV. EFFECTS

A. Carcinogenicity

Specific information on the carcinogenicity of chloral was not found in the available literature. However, Keith (1976) reported skin tumors in 4 of 20 mice dermally exposed to chloral hydrate (4 to 5 percent solution in acetone). Further interpretation of the results and discussion of the study methodology were not given.

B. Mutagenicity, Teratogenicity, and Other Reproductive Effects

Specific information on the mutagenicity, teratogenicity, and reproductive effects of chloral was not found in the available literature.

C. Chronic Effects

Rats receiving 0.1 mg/kg chloral exhibited a reduction of kidney function and serum transaminase after seven months' exposure (Kryatov, 1970). No physiological effects were observed in rats receiving 0.01 mg/kg chloral for periods of seven months. The route of exposure was not reported.

Chronic respiratory exposure of rats and rabbits to chloral at 0.1 mg/l (100 mg/m^3) produced changes in central nervous system function, decreased antitoxic and enzyme synthesizing function of the liver, and altered morphological characteristics of peripheral blood (Pavlova, 1975). Boitsov, et al. (1970) reported slowed growth rate, leukocytosis, decreased albumin-globulin ratio, and changes in arterial blood pressure and central nervous system responses (unspecified) following prolonged respiratory exposure of mice to chloral at 60 mg/m^3.

Goodman and Gilman (1970) reported gastritis, skin eruptions, and parenchymatous renal injury in patients suffering from chronic chloral hydrate intoxication. Habitual use of chloral hydrate may result in the

development of tolerance, physical dependence, and addiction. Death may occur either as a result of an overdose or a failure of the detoxification mechanism due to hepatic damage.

F. Acute Toxicity

According to Hann and Jensen (1974), the human acute oral LD_{50} of chloral is between 50 and 500 mg/kg.

Kryatov (1970) reported the following LD_{50} values for chloral: mice, 0.850 g/kg; rats, 0.725 g/kg; and guinea pigs, 0.940 g/kg. The routes of exposure were not stated. Verschueren (1977) reported an oral LD_{50} for rats of 0.05 to 0.4 g/kg, while Pavlov (1975) reported an acute oral LD_{50} of 0.94 and 1.34 g/kg for mice and rats, respectively. Pavlov (1975) also reported inhalation LC_{50} values of 25.5 g/m^3 and 44.5 g/m^3 for mice and rats, respectively. Boitsov, et al. (1970) reported an LD_{50} of 0.710 g/kg in mice. The route of exposure was not stated. Hawley (1971) reported that chloral is a highly toxic, strong irritant and noted ingestion or inhalation may be fatal. Information on acute toxic effects from occupational exposure to chloral was not found in the available literature.

G. Other Relevant Information

Verschueren (1977) reported an odor threshold concentration of chloral in water of 0.047 ppm. The author also reported an inhibition of cell multiplication in Pseudomonas sp. at a chloral hydrate concentration of 1.6 mg/l.

V. AQUATIC TOXICITY

A. Acute Toxicity

Verschueren (1977) reported inhibition of cell multiplication in Microcystis sp. at 78 mg/l chloral hydrate. Hann and Jensen (1974) ranked the 96-hour TL_m aquatic toxicity of chloral in the range from 1 to 10 ppm.

B. Chronic Toxicity

Information on the chronic aquatic toxicity of chloral was not found in the available literature.

C. Plant Effects

Shimizu, et al. (1974) reported chloral inhibited the growth of rice stems by 63.4 percent relative to controls, but slightly stimulated root growth. The concentration of chloral in water culture was not reported.

D. Residue

Keith (1976) identified chloral hydrate in chlorinated drinking water in six of ten cities sampled. The sample locations and concentrations of chloral hydrate identified were: Philadelphia, PA, 5.0 µg/l; Seattle, WA, 3.5 µg/l; Cincinnati, OH, 2.0 µg/l; Terrebonne Parish, LA, 1.0 µg/l; New York City, NY, 0.02 µg/l; Grand Forks, ND, 0.01 µg/l.

E. Other Relevant Information

Hann and Jensen (1974) ranked the aesthetic effect of chloral on water as very low (zero), noting that the chemical neither pollutes waters nor causes aesthetic problems.

VI. EXISTING GUIDELINES AND STANDARDS

Boitsov, et al. (1970) reported a maximum recommended chloral concentration in workroom air of 0.22 mg/l (220 mg/m^3) (USSR). Kryatov (1970) reported a maximum recommended permissible concentration in bodies of water as 0.2 mg/l (USSR). Verschueren (1977) reported a maximum allowable chloral concentration of 0.2 mg/l in Class I waters used for drinking, but the nation applying this standard was not identified.

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No. 35

Chlordane

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated chlordane and has found sufficient evidence to indicate that this compound is carcinogenic.

CHLORDANE

Summary

Chlordane is an organochlorinated cyclodiene insecticide commonly used as a formulation consisting of 24% trans-, 19% cis-chlordane, 10% heptachlor, 21.5% chlordenes, 7% nonachlor, and 18.5% of other organochlorinated material. Since heptachlor is also an insecticide and is more toxic than chlordane, technical chlordane is generally more toxic than pure chlordane.

Pure chlordane, which is a cis/trans mixture of isomers, induces liver cancer in mice and is mutagenic in some assays. Chlordane has not been shown to be teratogenic. Little information is available on chronic mammalian toxicity. Repeated doses of chlordane produced alterations in brain potentials and changes in some blood parameters. Chlordane is a convulsant. Chlordane and its toxic metabolite oxychlordane accumulate in adipose tissue.

Ten species of freshwater fish have reported 96-hr LC_{50} values ranging from 8 to 1160 µg/l. Freshwater invertebrates appear to be more resistant to chlordane, with observed 96-hr LC_{50} values ranging from 4 to 40 µg/l. Five species of saltwater fish have LC_{50} values of 5.5 to 160 µg/l, and marine invertebrate LC_{50} values range between 0.4 and 480 µg/l. Chronic studies involving the bluegill Daphnia magna gave an LC_{50} of 1.6 µg/l.

CHLORDANE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Chlordane (U.S. EPA, 1979).

Chlordane is a broad spectrum insecticide of the group of organochlorinated polycyclic hydrocarbons called cyclodiene insecticides. Chlordane has been used extensively over the past 30 years for termite control in homes and gardens, and as a control for soil insects.

Pure chlordane (1,2,4,5,6,7,8,8-octachloro-2,3,3a,4,7,7a-hexahydro-4,7-methanoindene) is a pale yellow liquid having the empirical formula $C_{10}H_6Cl_8$ and a molecular weight of 409.8. It is composed of a mixture of stereoisomers, with the cis- and trans- forms predominating, commonly referred to as alpha- and gamma-isomers, respectively.) The solubility of pure chlordane in water is approximately 9 µg/l at 25°C (U.S. EPA, 1979).

Technical grade chlordane is a mixture of chlorinated hydrocarbons with a typical composition of approximately 24 percent trans(gamma)-chlordane, 19 percent cis(alpha)-chlordane, 10 percent heptachlor (another insecticidal ingredient), 21.5 percent chlordene isomers, 7 percent nonachlor, and 18.5 percent closely related chlorinated hydrocarbon compounds. Technical chlordane is a viscous, amber-colored liquid with a cedar-like odor. It has a vapor pressure of 1×10^{-5} mm Hg at 25°C. The solubility of technical chlordane in water is 150 to 220 µg/l at 22°C (U.S. EPA, 1979).

Production of chlordane was 10,000 metric tons in 1974 (41 FR 7559; February 19, 1976). Both uses and production volume have declined extensively since the issuance of a registration suspension notice by the U.S. EPA (40 FR34456; December 24, 1975) for all food, crop, home, and garden

uses of chlordane. However, use of chlordane for termite control and limited usage (through 1980) as an agricultural insecticide are still permitted (43 FR 12372; March, 1978).

Chlordane persists for prolonged periods in the environment (U.S. EPA, 1979). Photo-cis-chlordane can be produced in water and on plant surfaces by the action of sunlight (Benson, et al. 1971) and has been found to be twice as toxic as chlordane to fish and mammals (Ivie, et al. 1972; Podowski, et al. 1979). Photo-cis-chlordane (5 ng/l) is accumulated more (ca. 20%) by goldfish (Carassius auratus) than chlordane (5 ng/l) itself (Ducat and Khan, 1979).

Air transport of chlordane has been hypothesized to account for residues in Sweden (Jansson, et al. 1979). Residues in agricultural soils may be as high as 195 ng/g dry weight of soil (Requejo, et al. 1979).

II EXPOSURE

A. Water

Chlordane has been detected in finished waters at a maximum concentration of 8 µg/l (Schafer, et al. 1969) and in rainwater (Bevenue, et al. 1972; U.S. EPA, 1976). There have been reports of individual household wells becoming contaminated after a house is treated with chlordane for termite control (U.S. EPA, 1979). A recent contamination of a municipal water system has been discussed by Harrington, et al. (1978). Chlordane has also been detected in rainwater (U.S. EPA, 1976).

B. Food

Chlordane has been found infrequently in food supplies since 1965, when the FDA began systematic monitoring for chlordane (Nisbet, 1976). The only quantifiable sample collected was 0.059 mg chlordane/kg measured in a sample of grain in 1972 (Manske and Johnson, 1975). In the most recently

published results (for 1975), chlordane was not detected (Johnson and Manske, 1977). Fish are thought to represent the most significant dietary exposure. The average daily uptake from fish is estimated at 1 µg (Nisbet, 1976).

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for chlordane to be 5,500 for the edible portions of fish and shellfish consumed by Americans. This estimate was based on measured steady-state bioconcentration studies in the sheepshead minnow (Cyprinodon variegatus).

Eighty-seven percent of 200 samples of milk collected in Illinois from 1971 to 1973 were positive for chlordane. The average concentration was 50 µg/l (Moore, 1975 as reviewed by Nat. Acad. Sci., 1977). Cyclodienes, such as chlordane, apparently are ingested with forage and tend to concentrate in lipids. Oxychlordane, a metabolite of chlordane and heptachlor, was found in 46 percent of 57 human milk samples collected during 1973-74 in Arkansas and Mississippi. The mean value was 5 µg/l, and the maximum was 20 µg/l (Strassman and Kutz, 1977).

C. Inhalation

In a survey of the extent of atmospheric contamination by pesticides, air was sampled at nine localities representative of both urban and agricultural areas. Chlordane was not detected in any samples (Stanley, et al. 1971). In a larger survey, 2,479 samples were collected at 45 sites in 16 states. Chlordane was detected in only two samples, with concentrations of 84 and 204 ng/m^3 (Nisbet, 1976). The vapor concentrations to which spray operators are exposed have not been estimated.

D. Dermal Effects

Chlordane can be absorbed through the skin to produce toxic effects (Gosselin, et al. 1976). Spray operators, chlordane formulators and farmers may be exposed. Chlordane has been known to persist for as long as two years on the hands (Kazen, et al. 1974). Dermal LD_{50} values in rats range from 530 to 700 mg/kg (U.S. EPA, 1979).

III. PHARMACOKINETICS

A. Absorption

Gastrointestinal absorption of chlordane in rats ranged from 6 percent with a single dose to 10-15 percent with smaller daily doses (Barnett and Dorough, 1974).

B. Distribution

In a study of the distribution of chlordane and its metabolites using radioactive carbon, the levels of residues in the tissues were low, except in the fat (Barnett and Dorough, 1974). Rats were fed 1, 5, and 25 mg chlordane/g in food for 56 days. Concentrations of chlordane residues in fat, liver, kidney, brain, and muscle were 300, 12, 10, 4, and 2 percent, respectively, of the concentration in the diet. All residues declined steadily for 4 weeks, at which time concentrations were reduced about 60 percent. During the next four weeks, residues declined only slightly.

C. Metabolism

Mammals metabolize chlordane to oxychlordane, via 1,2-dichloro-chlordene which is about twenty times more toxic than the parent compound and persists in adipose tissue (Polen, et al. 1971; Tashiro and Matsumura, 1978; Street and Blau, 1972). Oxychlordane can degrade to form 1-hydroxy-2-cyclochlordenes, and 1-hydroxy-2-chloro-2,3-epoxy-chlordenes (Tashiro and Matsumura, 1978). In general, the metabolism of chlordane takes place via a

series of oxidative enzyme reactions. None of the metabolic intermediates (except for oxychlordane) and end products are more toxic than chlordane (Barnett and Dorough, 1974; Tashiro and Matsumura, 1977; Mastri, et al. 1969). Trans-nonachlor, a major impurity in technical chlordene, is converted to trans-chlordane in rats, but this is not important in humans. This explains the fact that trans-nonachlor accumulates in humans but not in rats (Tashiro and Matsumura, 1978). A very small amount of cis- or trans-chlordane can be converted to heptachlor in rat liver (Tashiro and Matsumura, 1977).

D. Excretion

Chlordane is primarily excreted in the feces of rats, only about six percent of the total intake being eliminated in the urine. Urinary excretion of chlordane in rabbits is greater than excretion in the feces (Nye and Dorough, 1976).

The half-life of chlordane in a young boy was reported to be approximately 21 days (Curley and Garrettson, 1969), while for rats it was 23 days (Barnett and Dorough, 1974). The half-life of chlordane in the serum of a young girl was 88 days (Aldrich and Holmes, 1969).

IV. EFFECTS

A. Carcinogenicity

Hepatocellular carcinomas were induced in both sexes of two strains of mice fed pure (95%) chlordane (56.2 mg/kg) in the diet for 80 weeks (National Cancer Institute, 1977; Epstein, 1976). In contrast to findings with mice, a significantly increased incidence of hepatocellular carcinomas did not appear in rats administered chlordane. Dosages were near the maximum permissible (National Cancer Institute, 1977).

B. Mutagenicity

Pure or technical chlordane induced unscheduled DNA synthesis in the SV-40 transformed human fibroblast cell line VA-4. Metabolic activation eliminated this effect (Ahmed, et al. 1977). Chlordane did not induce mutations in the dominant lethal assay in mice (Arnold, et al. 1977).

While neither pure cis-chlordane nor pure trans-chlordane was mutagenic in the Ames Salmonella microsome assay, technical grade chlordane was mutagenic. Microsomal activation did not enhance the mutagenic activity (Simmon, et al. 1977).

C. Teratogenicity

Chlordane was found not to be teratogenic in rats when fed at concentrations of 150 to 300 mg/kg during gestation (Ingle, 1952).

D. Other Reproductive Effects

Pertinent data could not be located in the available literature.

E. Chronic Toxicity

There appears to be little information on chronic mammalian toxicity. Daily injections of 0.15 to 25 mg chlordane/kg in adult rats resulted in dose-dependent alterations of brain potentials (Hyde and Falkenberg, 1976). As changes were directly related to length of exposure, it was concluded that chlordane may be a cumulative neurotoxin. Length of exposure was not specified. Repeated doses of chlordane given to gerbils produced changes in serum proteins, blood glucose, and alkaline and acid phosphatase activities (Karel and Saxena, 1976). Again, duration of treatment was not specified.

F. Other Relevant Information

Carbon tetrachloride produced more extensive hepatocellular necrosis in chlordane-pretreated rats than in rats which were not pretreated (Stenger, et al. 1975). Rats suffered greater cirrhosis when chlordane (50

µg/kg/day) exposure for ten weeks followed prior exposures of ten weeks for carbon tetrachloride above (110 mg/l) or with chlordane (Mahon and Oloffs, 1979). Quail treated with chlordane followed by endrin had considerably more chlordane residues in their brains than did quail treated with chlordane alone (Ludke, 1976). Quail pretreated with 10 mg/kg chlordane exhibited decreased susceptibility to parathion (Ludke, 1977). Chlordane is a convulsant and emetic. It induces twitching, seizures and electroencephalographic dysrhythmia in humans. Acute symptoms can be alleviated with phenobarbital. Acute oral LD_{50} values for the rat range from 100 to 112 mg/kg (U.S. EPA, 1979). The no observable effect level was found to be 2.5 mg/kg/day over 15 days (Natl. Acad. Sci., 1977).

Chlordane inhibits growth of human viridans streptococci of the buccal cavity. Complete inhibition of growth occurred at 3 ppm, and about 20 percent inhibition was seen at 1 ppm (Goes, et al. 1978).

V. AQUATIC TOXICITY

A. Acute Toxicity

Ten species of freshwater fish have reported 96-hr LC_{50} values ranging from 8 to 1160 µg/l resulting from technical and pure chlordane exposure with a geometric mean of 16 µg/l. Rainbow trout, Salmo gairdneri (Mehrle, et al. 1974) was the most sensitive species tested, the channel catfish (Ictalurus punctatus) the least sensitive. The freshwater invertebrates were more sensitive to chlordane, with a reported LC_{50} value ranging from 4.0 for freshwater shrimp Palaemonetes kadiakensis (Sanders, 1972) to 40 µg/l (Gammarus fasciatus), with a geometric mean of 0.36 µg/l. In goldfish (Carassius auratus), only 0.13 percent of cis-chlordane is metabolized in 24 hours. Only 0.61 percent is converted after 25 days. Some metabolites were chlordene chlorohydrin and monohydroxy derivatives (Feroz and Khan, 1979).

The LC_{50}'s for four species of saltwater fish, sheepshead minnows (Cyprinodon variegatus), striped bass (Morone saxatilis), pinfish (Lagodon rhomboides), and white mullet (Mugil curema), ranged from 5.5 to 24.- µg/l. The three-spine stickleback (Gasterosteus aculeatus) yielded 96-hr LC_{50} values which ranged from 90-160 µg/l (Katz, 1961). Invertebrate LC_{50} values ranged from 0.4 for the pink shrimp, Penaeus duorarum (Parrish, et al. 1976) to 480 µg/l. The geometric mean of the adjusted LC_{50} values for invertebrates was 0.18 µg/l (U.S. EPA, 1979).

B. Chronic Toxicity

In a life cycle bioassay involving freshwater organisms, the chronic values for the bluegill Lepomis macrochirus (Cardwell, et al. 1977) was 1.6 µg/l. In two tests involving the sheepshead minnow, Cyprinodon variegatus, the chronic values were 0.63 µg/l for the life cycle test (Parrish, et al. 1978) and 5.49 µg/l for an embryo-level test (Parrish, et al. 1976).

Many blood parameters (clotting time, mean corpuscular hemoglobin and cholesterol level) are lowered after the teleost, Sacco-branchus fossilus, is exposed to 120 µg/l of chlordane for 15 to 60 days (Verna, et al. 1979). Similar results were obtained in Labeo rohita at doses $\geq$ 23 µg/l after 30 to 60 day exposures (Bansal, et al. 1979).

C. Plant Effects

A natural saltwater phytoplankton community suffered a 94 percent decrease in productivity during a 4-hour exposure at 1,000 µg/l (Butler, 1963).

D. Residues

In Daphnia magna, chlordane was bioconcentrated 6,000-fold after seven days' exposure and 7,400-fold by scuds (Hyallela azteca) after 85 days of exposure (Cardwell, et al. 1977). After 33 days' exposure, the fresh-

water alga (Oedegonium sp.) bioconcentrated chlordane 98,000-fold; Physa sp., a snail, concentrated it 133,000-fold (Sanborn, et al. 1976). Equilibrium bioconcentration factors for the sheepshead minnow ranged from 6,580 to 16,035 (Goodman, et al. 1978; Parrish, et al. 1976).

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The issue of the carcinogenicity of chlordane in humans is being reconsidered; thus, there is a possibility that the criterion for human health will be changed. Based on the data for carcinogenicity in mice (Epstein, 1976), and using the "one-hit" model, the U.S. EPA (1979) has estimated levels of chlordane in ambient water which will result in risk levels of human cancer as specified in the table below.

Exposure Assumptions (per day)	Risk Levels and Corresponding Draft Criteria			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish.	0	0.012 ng/l	0.12 ng/l	1.2 ng/l
Consumption of fish and shellfish only.	0	0.013 ng/l	0.13 ng/l	1.3 ng/l

The ACGIH (1977) adopted a time-weighted average value of 0.5 mg/m^3 for chlordane, with a short-term exposure limit (15 minutes) of 2 mg/m^3.

A limit of 3 µg/l for chlordane in drinking water is suggested under the proposed Interim Primary Drinking Water Standards (40 FR 11990, March 14, 1975).

Canadian Drinking Water Standards (Dept. Natl. Health Welfare, 1968) limit chlordane to 3 µg/l in raw water supplies.

B. Aquatic

For chlordane, the proposed criterion to protect freshwater aquatic life is 0.024 µg/l for a 24-hour average, not to exceed 0.36 µg/l at any time (U.S. EPA, 1979). For saltwater aquatic species, the draft criterion is 0.0091 µg/l for a 24-hour average, not to exceed 0.18 µg/l at any time (U.S. EPA, 1979).

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Chlorinated Benzenes

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OCTOBER 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

CHLORINATED BENZENES

Summary

The chlorinated benzenes are a group of compounds with a wide variety of physical and chemical characteristics depending on the degree of chlorination. As chlorination increases, the persistence of the compound in the environment increases. On chronic exposure liver and kidney changes are noted, and the degree of toxicity increases with the degree of chlorination. The chlorinated benzenes have not been shown to be teratogens or mutagens. Only hexachlorobenzene has been demonstrated to be carcinogenic in laboratory animals.

Aquatic toxicity data indicate a trend to increasing toxicity with increasing chlorination for all species tested. For the bluegill, for example, the following 96-hour LC_{50} values; have been noted: chlorobenzene, 15,900 ug/l; 1,2,4-trichlorobenzene, 200 ug/l. Other freshwater and saltwater fish, invertebrates and plants are generally less sensitive to chlorobenzenes than the bluegill. The sheephead minnow yielded a chronic value of 14.5 ug/l for 1,2,4,5tetrachlorobenzene in an embryo-level test. After 28 days of exposure, the bioconcentration factors for the bluegill for pentachlorobenzene and 1,2,4,5-tetrachlorobenzene were 3,400 and 1,800, respectively.

CHLORINATED BENZENES

I. INTRODUCTION

This profile is based inpart on the Ambient Water Quality Criteria Document for Chlorinated Benzenes (U.S. EPA, 1980). This document summarizes the general properties of the chlorinated benzenes. For further information on monochlorobenzene, 1,2,4-trichlorobenzene, or hexachlorobenzene, refer to the specific EPA/ECAO Hazard Profiles for these compounds. For detailed information on the other chlorinated benzenes refer to the Ambient Water Quality Document (U.S. EPA, 1980).

The chlorinated benzenes, excluding dichlorobenzenes*, are monochlorobenzene (C_6H_3Cl), 1,2,4-trichlorobenzene ($C_6H_3Cl_3$), 1,3,5-trichlorobenzene ($C_6H_3Cl_3$), 1,2,3,4-tetrachlorobenzene ($C_6H_2Cl_4$), 1,2,3,5-tetrachlorobenzene ($C_6H_2Cl_4$), 1,2,4,5-tetrachlorobenzene ($C_6H_2Cl_4$), pentachlorobenzene (C_6Cl_5) and hexachlorobenzene (C_6Cl_6). All chlorinated benzenes are colorless liquids or solids with a pleasant aroma. The most important properties imparted by chlorine to these compounds are solvent power, viscosity and moderate chemical reactivity. Viscosity and nonflammability tend to increase with degree of chlorination. Vapor pressures and water solubility decrease progressively with the degree of chlorination (U.S. EPA, 1980).

*the health and environmental effects of dichlorobenzenes are discussed in HEBD's Nos. 64-67.

The current production, based on annual production in the U.S., was 139,105 kkg of monochlorobenzene in 1975, 12,849 kkg of 1,2,4-trichlorobenzene, 8,182 kkg of 1,2,4,5-tetrachlorobenzene and 318 kkg of hexachlorobenzene in 1973 (West and Ware, 1977; EPA, 1975a). The remaining chlorinated benzenes are produced mainly as by-products from the production processes for the above four chemicals. Chlorinated benzenes have many and diverse uses in industry depending upon the individual properties of the specific compound. Some uses are as solvents, chemical intermediates, flame retardants, and plasticizers.

II. EXPOSURE

A. Water

Mono-, tri-, and hexachlorobenzene have been detected in ambient water. Because of its high volatility, monochlorobenzene has a short half-life of only 5.8 hours (Mackay and Leinonen, 1975). However, hexachlorobenzene has an extremely long residue time in water, appearing to be ubiquitous in the aqueous environment. Monochlorobenzene has been detected in "uncontaminated" water at levels of 4.7 ug/l. Both trichlorobenzene and hexachlorobenzene have been detected in drinking waters at concentrations of 1.0 ug/l and 4 to 6 ng/l respectively (U.S. EPA, 1980). There is no information available on the concentration of the other chlorinated benzenes in water.

B. Food

There is little data on the consumption of chlorinated benzenes in food. All the chlorinated benzenes appear to

concentrate in fat, and can be absorbed by plants from contaminated soil. Both pentachlorobenzene and hexachlorobenzene have been detected in meat fat (e.g. Stijve, 1971; Ushio and Doguchi, 1977). Hexachlorobenzene, the most extensively studied compound, has been found in a wide variety of foods from cereals to milk (including human breast milk), eggs, and meat. The U.S. EPA (1980) has estimated the weighted bioconcentration factors for freshwater species:

Chemical	Weighted bioconcentration factor
monochlorobenzene	13
1,2,4-trichlorobenzene	182
1,2,3,5-tetrachlorobenzene	1,800
pentachlorobenzene	3,400
hexachlorobenzene	22,000

These estimates were based on the octanol/water partition coefficients of the chlorinated benzenes.

C. Inhalation

There is no available data on the concentration of chlorinated benzenes in ambient air with the exception of measurements of aerial fallout of particulate bound 1,2,4-trichlorobenzene in southern California. Five sampling sites showed median levels of 1,2,4-trichlorobenzene of less than 11 ng/m^2/day (U.S. EPA, 1980). The primary site of inhalation exposure to chlorinated benzenes is the workplace in industries utilizing and/or producing these compounds.

III. PHARMACOKINETICS

A. Absorption

There is little data on the absorption of orally administered chlorinated benzenes. It is apparent from the

toxicity of orally administered compounds that absorption does take place, and tetrachlorobenzene has been shown to be absorbed relatively efficiently by rabbits (Jondorf, et al. 1958). Pentachlorobenzene was absorbed poorly after subcutaneous injection (Parke and Williams, 1960). Hexachlorobenzene was absorbed poorly from an orally administered aqueous solution (Koss and Kornasky, 1975), but with high efficiency when administered in oil (Albro and Thomas, 1974). The more highly chlorinated compounds in food products selectively partition into the lipid portion and are absorbed far better than those in the aqueous portion (U.S. EPA, 1980).

B. Distribution

The chlorinated benzenes are lipophilic compounds, with greater lipophilic tendencies in the more highly chlorinated compounds. The predominant uptake site is either suspected or known to be the lipid tissues of the body (Lee and Metcalf, 1975; U.S. EPA, 1980).

C. Metabolism

The chlorinated benzenes are metabolized in the liver by the NADPH-cytochrome P-448 dependent microsomal enzyme system (Ariyoshi, et al. 1975; Koss, et al. 1976). At least for monochlorobenzene, there is evidence that toxic intermediates are formed during metabolism (Kohli, et al. 1976). Various conjugates and phenolic derivatives are the primary excretory end products of chlorinated benzene metabolism. Conjugates of the more highly chlorinated compounds, such as hexachlorobenzene, are only formed to a limited extent, and their metabolism is relatively slow.

D. Excretion

The less-chlorinated benzenes are excreted as polar metabolites or conjugates in the urine. An exception occurs with monochlorobenzene is an exception: in the rabbit, 27 percent of an administered dose appeared as unchanged compounds in expired air (Williams, 1959). The two highly chlorinated compounds, pentachlorobenzene and hexachlorobenzene, are predominately eliminated in unchanged form by fecal excretion (Koss and Koransky, 1975; Rozman, et al. 1979). The biological half-lives of these two compounds are extremely long in comparison to those of the less-chlorinated compounds (U.S. EPA, 1980).

IV. EFFECTS

A. Carcinogencity

The carcinogenic potential of mono- and tetrachlorobenzene have not been investigated (U.S. EPA, 1980). In one study, trichlorobenzene was not shown to produce any significant increase in liver tumors (Gotto, et al. 1972). There is one report, not critically evaluated by EPA (1980), which alludes to the carcinogencity of pentachlorobenzene in mice and the absence of this activity in rats and dogs (Preussman, 1975). Life-time feeding studies in hamsters (Cabral, et al. 1977) and mice (Cabral, et al. 1978) have demonstrated the carcinogenic activity of hexachlorobenezene. However, shorter term studies failed to demonstrate an increased tumor incidence in strain A mice or ICR mice (Theiss, et al. 1977; Shirai, et al. 1978). Chlorobenzene has been tentatively selected for long-term bioassay testing by NCI (U.S. EPA, 1978b).

B. Mutagenicity

There are no reports of studies conducted to evaluate the mutagenic potential of tri-,tetra- and pentachlorobenzene. Chlorobenzene causes mutations in S.antibioticus, and chromosomal damage and mitotic inhibition in root tips of higher plants, and is not mutagenic in the fungus A.nidulans (U.S. EPA, 1978b). Hexachlorobenzene was assayed for mutagenic activity in the dominant lethal assay, and shown to be inactive (Khera, 1974).

C. Teratogenicity

There are no available reports on the teratogenic potential of mono-, tri-, and tetra-, chlorobenzene (U.S. EPA, 1980). Khera (1974) concluded that hexachlorobenzene is not a teratogen when given to CD-1 mice at 50 mg/kg/day on gestation days from 7 to 11. Pentachlorobenzene, however, induces a dose-related incidence of sternebral defects in rats (Khera, 1975).

D. Other Reproductive Effects

Both penta- and hexachlorobenzene pass through the placenta and cause fetal toxicity in rats (Grant, et al. 1977). The distribution of hexachlorobenzene in the fetus appears to be the same as in the adult, with the highest concentration in fatty tissue.

E. Chronic Toxicity

There are no available data on the chronic effects of pentachlorobenzene (U.S. EPA, 1979). Mono- and trichlorobenzene product histological changes in the liver and kidney (Irish, 1963; Coate, et al. 1977). Chlorobenzene (orally administered at 250 mg/kg for 3 days) caused liver dysfunction and porphyria

(U.S. EPA, 1978b). There is also evidence for liver damage occurring with prolonged exposure of rats and dogs to tetrachlorobenzene (Fomenko, 1965; Braun, et al. 1978). Hexachlorobenzene has caused histological changes in the livers of rats (Koss, et al. 1978). In humans exposed to undefined amounts of hexachlorobenzene for an undetermined time, porphyrinuria has been shown to occur (Cam and Nigogosyan, 1963).

F. Other Relevant Information

Chlorinated benzenes appear to increase the activity of microsomal NADPH-cytochrome P-450 dependent enzyme systems.

V. ACUATIC TOXICITY (U.S. EPA, 1980)

A. Acute Toxicity

The dichlorobenzenes are covered in a separate EPA/ECAO hazard profile and will not be covered in this disucssion on chlorobenzenes.

All data reported for freshwater fish are from 96-hour static toxicity tests. Pickering and Henderson (1966) reported 96-hour LC_{50} values for goldfish, guppies and bluegills to be 51,620, 45,530, and 24,000 ug/l, respectively, for chlorobenzene. Two 96 hour LC_{50} values for chlorobenzene and fathead minnows are 33,930 ug/l in saltwater and 29,120 ug/l in hard water. Reported 96-hour values for the bluegill exposed to chlorobenzene, 1,2,4-trichlorobenzene, 1,2,3,5- and 1,2,4,5-tetrachlorobenzenes and pentachlorobenzene are 15,900, 3,360, 6,420, 1,550, and 250 ug/l, respectively (U.S. EPA, 1978). These data indicate increasing toxicity with chlorination, except for monochlorobenzene. EC_{50} (48 hour) values reported for Daphnia magna are: chlorobenzene

86,000 ug/l, 1,2,4-trichlorobenzene 50,200 ug/l, 1,2,3,5-tetrachlorobenzene 9,710 ug/l, and pentachlorobenzene 5,280 ug/l.

Toxicity tests with the sheepshead minnow, Cyprinodon variegatus, performed with five chlorinated benzenes under static conditions and yielded the following 96-hour LC_{50} values: chlorobenzene 10,500 ug/l, 1,2,4-trichlorobenzene 21,400 ug/l, 1,2,3,5-tetrachlorobenzene 3,670 ug/l, 1,2,4,5 tetrachlorobenzene 840 ug/l, and pentrachlorobenzene 835 ug/l. As with sheepshead minnows, sensitivity of the mysid shrimp, Mysidopsis bahia, to chlorinated benzenes generally increases with increasing chlorination. The reported 96-hour LC_{50} values are as follows: chlorobenzene 16,400 ug/l, 1,2,4-trichlorobenzene 450 ug/l, 1,2,3,5-tetrachlorobenzene 340 ug/l, 1,2,4,5-tetrachlorobenzene 1,480 ug/l, and 160 ug/l for pentachlorobenzene.

B. Chronic Toxicity

Chronic toxicity data are not available for freshwater fish or invertebrate species. Only one saltwater species, Cyprinodon variegatus, has been chronically exposed to any of the chlorinated benzenes. In an embryo-level test, the limits for 1,2,4,5-tetrachlorobenzene are 92 to 180 ug/l, with a final chronic value of 64.5 ug/l.

C. Plant Effects

The green freshwater algae Selenastrum capricornutum has been exposed to five chlorinated benzenes. Based on cell number, the 96-hour EC_{50} values are as follows: chlorobenzene 220,000 ug/l, 1,2,4-trichlorobenzene 36,700 ug/l, 1,2,3,5-tetrachlorobenzene 17,700 ug/l, 1,2,4,5-tetrachlorobenzene 46,800

ug/l, and pentachlorobenzene 6,780 ug/l.

D. Residues

No measured bioconcentration factor (BCF) is available for chlorobenzenes. However, the average weighted BCF of 13 was calculated from octanol-water partition coefficient and other factors (See above) (U.S. EPA, 1980).

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

Monochlorobenzene: The American Conference of Governmental Industrial Hygienists (ACGIH, 1971) threshold limit value for monochlorobenzene is 75 ppm. The U.S. EPA ambient water quality criterion for monochlorobenzene is 20 ug/l based on the threshold concentration for odor and taste, and 488 ug/l based on its toxic effects (U.S. EPA, 1980).

Trichlorobenzene: The American Conference of Governmental Industrial Hygienists (ACGIH, 1977) threshold limit value for 1,2,4-trichlorobenzene is (5 ppm). Because of the insufficiency of available information for trichlorobenzene U.S. EPA (1980) determined that a criterion could not be derived using the guidelines in effect in 1980.

Tetrachlorobenzene: The U.S. EPA (1980) ambient water quality criterion for 1,2,4,5-tetrachlorobenzene based on its toxic effects, is 38 ug/l.

Pentachlorobenzene: The U.S. EPA (1979) ambient water quality criterion for pentachlorobenzene based on its toxic effects is 74 ug/l.

Hexachlorobenzene: The value of 0.6 ug/kg/day was suggested by FAO/WHO as a reasonable upper limit for residues in food for human consumption (FAO/WHO, 1974). The Louisiana State Department of Agriculture has set the tolerated level of hexachlorobenzene in meat fat at 0.3 mg/kg (U.S. EPA, 1976). The FAO/WHO recommendations for residues in foodstuffs were 0.5 mg/kg in fat for milk and eggs, and 1 mg/kg in fat for meat and poultry (FAO/WHO, 1974). For maximum protection of human health from the potential carcinogenic effects of hexachlorobenzene through ingestion of contaminated water and contaminated aquatic organisms, the ambient water criterion is 0.72 ug/l (10^{-7} incremental lifetime risk)(U.S. EPA, 1980).

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No. 37

Chlorinated Ethanes

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated chlorinated ethanes and has found sufficient evidence to indicate that this compound is carcinogenic.

CHLORINATED ETHANES

SUMMARY

Four of the chlorinated ethanes have been shown to produce tumors in experimental animal studies conducted by the National Cancer Institute (NCI). These four are 1,2-dichloroethane, 1,1,2-trichloroethane, 1,1,2,2-tetrachloroethane, and hexachloroethane. Animal tumors were also produced by administration of 1,1,1-trichloroethane, but this bioassay is being repeated due to premature deaths in one initial study.

Two of the chlorinated ethanes, 1,2-dichloroethane and 1,1,2,2-tetrachloroethane, have shown mutagenic activity in the Ames Salmonella assay and in E. coli. 1,2-Dichloroethane has also shown mutagenic action in pea plants and in Drosophila.

No evidence is available indicating that the chloroethanes produce teratogenic effects. Some toxic effects on fetal development have been shown following administration of 1,2-dichloroethane and hexachloroethane.

Symptoms produced by toxic exposure to the chloroethanes include central nervous system disorders, liver and kidney damage, and cardiac effects.

Aquatic toxicity data for the effects of chlorinated ethanes to freshwater and marine life are few. Acute studies have indicated that hexachloroethane is the most toxic of the chlorinated ethanes reviewed. Marine organisms tend to be more sensitive than freshwater organisms with acute toxicity values as low as 540 µg/l being reported.

CHLORINATED ETHANES

I. INTRODUCTION

This profile is based on the draft Ambient Water Quality Criteria Document for Chlorinated Ethanes (U.S. EPA, 1979).

The chloroethanes (see table 1) are hydrocarbons in which one or more of the hydrogen atoms have been replaced by chlorine atoms. Water solubility and vapor pressure decrease with increasing chlorination, while density and melting point increase. Monochloroethane is a gas at room temperature, hexachloroethane is a solid, and the remaining compounds are liquids. All chloroethanes show some solubility in water, and all, except monochloroethane, are more dense than water.

The chloroethanes are used as solvents, cleaning and degreasing agents, in the manufacture of plastics and textiles, and in the chemical synthesis of a number of compounds.

Current production:

monochloroethane	335×10^3	tons/yr in 1976
1,2-dichloroethane	$4{,}000 \times 10^3$	tons/yr in 1976
1,1,1-trichloroethane	215×10^3	tons/yr in 1976

The chlorinated ethanes form azeotropes with water (Kirk and Othmer, 1963). All are very soluble in organic solvents (Lange, 1956). Microbial degradation of the chlorinated ethanes has not been demonstrated (U.S. EPA, 1979).

II. EXPOSURE

The chloroethanes are present in raw and finished waters due primarily to industrial discharges. Small amounts of the chloroethanes may be formed by chlorination of drinking water or treatment of sewage. Water monitoring studies

have shown the following levels of various chloroethanes: 1,2-dichloroethane, 0.2-8 µg/l; 1,1,2-trichloroethane, 0.1-8.5 µg/l; 1,1,1,2-tetrachloroethane, 0.11 µg/l (U.S. EPA, 1979). In general, air levels of chloroethanes are produced by evaporation of volatile chloroethanes widely used as degreasing agents and in dry cleaning operations (U.S. EPA, 1979). Industrial monitoring studies have shown air levels of 1,1,1-trichloroethane ranging from 1.5 to 396 ppm (U.S. EPA, 1979).

TABLE 1

Chloroethanes and Synonyms

Compound Name	Synonyms	
Monochloroethane	Chloroethane	Ethyl chloride
1,1,-Dichloroethane	Ethylidene Dichloride	Ethylidene Chloride
1,2-Dichloroethane	Ethylene Dichloride	Ethylene Chloride
1,1,1-Trichloroethane	Methyl Chloroform	Chlorothene
1,1,2-Trichloroethane	Ethane Trichloride	Vinyl Trichloride
1,1,1,2-Tetrachloroethane	Tetrachloroethane	
1,1,2,2-Tetrachloroethane	Acetylene Tetrachloride	Sym-Tetrachloroethane
Pentachloroethane	Pentalin	Ethane Pentachloride
Hexachloroethane	Perchloroethane	

Sources of human exposure to chloroethanes include water, air, contaminated foods and fish, and dermal absorption. The two most widely used solvents, 1,2-dichloroethane and 1,1,1-trichloroethane, are the compounds most often detected in foods. Analysis of several foods indicated 1,1,1-trichloro-

ethane levels of 1-10 µg/kg (Walter, et al. 1976), while levels of 1,2-dichloroethane found in 11 of 17 species have been reported to be 2-23 µg/g (Page and Kennedy, 1975). Fish and shellfish have shown levels of chloroethanes in the nanogram range (Dickson and Riley, 1976).

The U.S. EPA (1979) has derived the following weighted average bioconcentration factors for the edible portions of fish and shellfish consumed by Americans: 1,2-dichloroethane, 4.6; 1,1,1-trichloroethane, 21; 1,1,2,2-tetrachloroethane, 18; pentachloroethane, 150; hexachloroethane, 320. These estimates were based on the measured steady-state bioconcentration studies in bluegill. Bioconcentration factors for 1,1,2-trichloroethane (6.3) and 1,1,1,2-tetrachloroethane (18) were derived by EPA (1979) using octanol-water partition coefficients.

III. PHARMACOKINETICS

A. Absorption

The chloroethanes are absorbed rapidly following ingestion or inhalation (U.S. EPA, 1979). Dermal absorption is thought to be slower in rabbits based on studies by Smyth, et al. (1969). However, rapid dermal absorption has been seen in guinea pigs with the same trichloroethane (Jakobson, et al. 1977).

Human studies on the absorption of inhaled 1,1,2,2-tetrachloroethane indicate that the compound is completely absorbed after exposure to trace levels of radiolabeled vapor (Morgan, et al., 1970, 1972). At higher exposure levels absorption is rapid in man and animals, but obviously not complete.

B. Distribution

Studies on the distribution of 1,1,1-trichloroethane in mice following inhalation exposure have shown levels in the liver to be twice that found in the kidney and brain (Holmberg, et al. 1977). Postmortem examination of human tissues showed 1,1,1-trichloroethane in body fat (highest concentration) kidneys, liver, and brain (Walter, et al. 1976). Due to the lipid solubility of chloroethanes, body distribution may be expected to be widespread. Stahl, et al. (1969) have noted that human tissue samples of liver, brain, kidney, muscle, lung, and blood contained 1,1,1-trichloroethane following acute exposure, with the liver containing the highest concentration.

Passage of 1,1,1,2-tetrachloroethane across the placenta has been reported by Truhaut, et al. (1974) in rabbits and rats.

C. Metabolism

The metabolism of chloroethanes involves both enzymatic dechlorination and hydroxylation to corresponding alcohols (Monster, 1979; Truhaut, 1972). Oxidation reactions may produce unsaturated metabolites which are then transformed to the alcohol and ester (Yllner, 1971 a,b,c,d).

Metabolism appears to involve the activity of the mixed function oxidase enzyme system (Van Dyke and Wineman, 1971). Animal experiments by Yllner (1971 a,b,c,d,e) indicated that the percentage of administered compound metabolized decreased with increasing dose, suggesting saturation of metabolic pathways.

D. Excretion

The chloroethanes are excreted primarily in the urine and in expired air (U.S. EPA, 1979). As much as 60 to 80 percent of an inhaled dose of 1,1,1-trichloroethane (70 or 140 ppm for 4 hours) was expired unchanged by human volunteers (Monster, et al. 1979). Animal studies conducted by Yllner (1971 a,b,c,d) indicate that largest amount of chloroethanes, administered by intraperitoneal (i.p.) injection is excreted in the urine; this is followed by expiration (in the changed or unchanged form), with very little excretion in the feces. Excretion appears to be rapid, since 90 percent of i.p. administered doses of 1,2-dichloroethane or 1,1,2-trichloroethane were eliminated in the first 24 hours (U.S. EPA, 1979). However, the detection of chloroethanes in postmortem tissue samples indicates that some portion of these compounds persists in the body (Walter, et al. 1976).

IV. EFFECTS

A. Carcinogenicity

Several chlorinated ethanes have been shown to produce a variety of tumors in rats and mice in experiments utilizing oral administration. Tumor types observed after compound administration include squamous cell carcinoma of the stomach, hemangiosarcoma, adenocarcinoma of the mammary gland, and hepatocellular carcinoma (NCI, 1978a,b,c,d). The four chlorinated ethanes which have been classified as carcinogens based on animal studies are: 1,2-dichloroethane, 1,1,2-trichloroethane, 1,1,2,2-tetrachloroethane,

and hexachloroethane. Increased tumor production was also noted in animals treated with 1,1,1-trichloroethane, but high mortality during this study (NCI, 1977) caused retesting of the compound to be initiated. In vitro transformation of rat embryo cells and subsequent fibrosarcoma production by these cells when injected in vivo, indicate that 1,1,1-trichloroethane does have carcinogenic potential (Price, et al. 1978).

B. Mutagenicity

Two of the chlorinated ethanes, 1,2-dichloroethane and 1,1,2,2-tetrachloroethane, have shown mutagenic activity in the Ames Salmonella assay and for DNA polymerase deficient strain of E. coli (Brem, et al. 1974). In these two systems, 1,1,2,2-tetrachloroethane showed higher mutagenic activity than 1,2-dichloroethane (Rosenkranz, 1977).

Mutagenic effects have been produced by 1,2-dichloroethane in pea plants (Kirichek, 1974) and in Drosophila (Nylander, et al. 1978). Several metabolites of dichloroethane (chloroacetaldehyde, chloroethanol, and S-chloroethyl cysteine have also been shown to produce mutations in the Ames assay (U.S. EPA, 1979).

Testing of hexachloroethane in the Ames Salmonella assay or in a yeast assay system failed to show any mutagenic activity (Weeks, et al. 1979).

C. Teratogenicity

Inhalation exposure of pregnant rats and mice to 1,1,1-trichloroethane was shown to produce some soft

tissue and skeletal deformities; this incidence was not judged statistically significant by the Fisher Exact probability test (Schwetz, et al. 1975).

Testing of hexachloroethane administered to rats by intubation or inhalation exposure did not show an increase in teratogenic effects (Weeks, et al. 1979). Inhalation exposure of pregnant rats to 1,2-dichloroethane also failed to demonstrate teratogenic effects (Schwetz, et al. 1974; Vozovaya, 1974).

D. Other Reproductive Effects

Decreased litter size, reduced fetal weights and a reduction in live births have been reported in rats exposed to 1,2-dichloroethane (57 mg/m^{3}m four hours/day, six days/week) by inhalation (Vozovaya, 1974). 1,1-Dichloroethane retarded fetal development at exposures of 6,000 ppm. (Schwetz, et al. 1974). Higher fetal resorption rates and a decreased number of live fetuses per litter were observed in rats following administration of hexachloroethane by intubation (15, 48 or 260 ppm, 6 hours/day) or inhalation (50, 100 or 500 mg/kg/day) (Weeks, et al. 1979).

E. Chronic Toxicity

Neurologic changes and liver and kidney damage have been noted following long term human exposure to 1,2-dichloroethane (NIOSH, 1978). Cardiac effects (overstimulation) have been noted following human exposure to 1,1-dichloroethane (U.S. EPA, 1979).

Central nervous system disorders have been reported in humans exposed to 1,1,1-trichloroethane. Symptoms noted

were altered reaction time, perceptual speed, manual dexterity, and equilibrium (U.S. EPA, 1979).

Animal studies indicate that the general symptoms of toxicity resulting from exposure to the chloroethanes involve effects in the central nervous system, cardiovascular system, pulmonary system, and the liver and kidney (U.S. EPA, 1979). Laboratory animals and humans exposed to chloroethanes show similar symptoms of toxicity (U.S. EPA, 1979).

Based on data derived from animal studies, the U.S. EPA (1979) has concluded that the relative toxicity of the chloroethanes is as follows: 1,2-dichloroethane > 1,1,2,2-tetrachloroethane > 1,1,2-trichloroethane > hexachloroethane 1,1-dichloroethane > 1,1,1-trichloroethane > monochloroethane.

F. Other Relevant Information

The hepatotoxicity of 1,1,2-trichloroethane was increased in mice following acetone or isopropyl alcohol pretreatment (Traiger and Plaa, 1974). Similarly, ethanol pretreatment of mice increased the hepatic effects of 1,1,1-trichloroethane (Klassen and Plaa, 1966).

Hexobarbital sleeping times in rats were reported to be decreased following inhalation exposure to 1,1,1-trichloroethane (3,000 ppm), indicating an effect of the compound on stimulation of hepatic microsomal enzymes (Fuller, et al. 1970).

V. AQUATIC TOXICITY

A. Acute Toxicity

Acute toxicity studies were conducted on three species of freshwater organisms and two marine species.

For freshwater fish, 96-hour static LC_{50} values for the bluegill sunfish, Lepomis macrochirus, ranged from 980 µg/l hexachloroethane to 431,000 µg/l 1,2-dichloroethane, while the range of 48-hour LC_{50} values for the freshwater invertebrate Daphnia magna was 8,070 µg/l to 218,000 µg/l for hexachloroethane and 1,2-dichloroethane respectively. Among marine organisms, the sheepshead minnow (Cyprinodon variegatus) produced LC_{50} values ranging from 2,400 µg/l for hexachloroethane to 116,000 µg/l for pentachloroethane. The marine mysid shrimp (Mysidopsis bahia) produced LC_{50} values ranging from 940 µg/l for hexachloroethane to 113,000 µg/l for 1,2-dichloroethane. The general order of acute toxicities for the chlorinated ethanes reviewed for freshwater fish is: hexachloroethane (highest toxicity), 1,1,2,2-tetrachloroethane, 1,1,2-trichloroethane, pentachloroethane, and 1,2-dichloroethane (U.S. EPA, 1979).

B. Chronic Toxicity

The only chronic study available for the chlorinated ethanes is for pentachloroethane's chronic effects on the marine shrimp (Mysidopsis bahia), which produced a chronic value of 580 µg/l (U.S EPA, 1978).

C. Plant Effects

Effective EC_{50} concentrations, based on chlorophyll a and cell numbers for the freshwater algae Selenastrum capriconutum ranges from 87,000 µg/l for hexachloroethane to 146,000 µg/l for 1,1,2,2-tetrachloroethane, with pentachloroethane being intermediate in its phytotoxicity. For the marine algae Skeletonema costatum, a greater sensi-

tivity was indicated by effective EC_{50}- concentrations based on cell numbers and chlorophyll a ranging from 6,230 µg/l for 1,1,2,2-tetrachloroethane and 7,750 µg/l for hexachloroethane to 58,200 µg/l for pentachloroethane.

D. Residues

The bioconcentration value was greatest for hexachloroethane with a value of 139 µg/l being reported for bluegill. Bioconcentration values of 2, 8, and 9 were obtained for 1,2-dichloro, 1,1,2,2-tetrachloro, and 1.1,1-trichloroethane for bluegills. 1,1,2-Trichloroethane and 1,1,1,2-tetrachloroethane used the octanol/water coefficients to derive BCF's of 22 and 62, respectively.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria may be changed.

A. Human

Based on the NCI carcinogenesis bioassay data, and using a linear, non-threshold model, the U.S. EPA (1979) has estimated levels of four chloroethanes in ambient water that will result in an additional cancer risk of 10^{-5}: 1,2-dichloroethane, 7.0 µg/l; 1,1,2-trichloroethane, 2.7 µg/l; 1,1,2,2-tetrachloroethane, 1.8 µg/l; hexachloroethane, 5.9 µg/l. A draft ambient water quality criterion to protect human health has been derived by EPA for 1,1,1-trichloroethane based on mammalian toxicity data at the level of 15.7 mg/l.

Insufficient mammalian toxicological data prevented derivation of a water criterion for monochloroethane, 1,1-dichloroethane, 1,1,1,2-tetrachloroethane, or pentachloroethane (U.S. EPA, 1979).

The following compounds have had eight hour, TWA exposure standards established by OSHA: monochloroethane, 1,000 ppm; 1,1-dichloroethane, 100 ppm; 1,2-dichloroethane, 50 ppm; 1,1,1-trichloroethane, 350 ppm; 1,1,2-trichloroethane, 10 ppm; 1,1,2,2-tetrachloroethane, 5 ppm; hexachloroethane, 1 ppm.

B. Aquatic

Criteria for protecting freshwater organisms have been drafted for five of the chlorinated hydrocarbons: 62 µg/l (average concentation) not to exceed 140 µg/l for hexachloroethane; 170 µg/l not to exceed 380 µg/l for 1,1,2,2-tetrachloroethane; 440 µg/l not to exceed 1,000 µg/l for pentachloroethane; 3,900 µg/l not to exceed 8,800 µg/l for 1,2-dichloroethane; and 5,300 µg/l not to exceed 12,000 µg/l for 1,1,1-trichloroethane. For marine organisms, criteria have been drafted as: 7 µg/l (average concentration) not to exceed 16 µg/l for hexachloroethane; 38 µg/l not to exceed 87 µg/l for pentachloroethane; 70 µg/l not to exceed 160 µg/l for 1,1,2,2-tetrachloroethane; 240 µg/l not to exceed 540 µg/l for 1,1,1-trichloroethane; and 880 µg/l not to exceed 2,000 µg/l for 1,2-dichloroethane.

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No. 38

Chlorinated Naphthalenes

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

CHLORINATED NAPTHALENES

Summary

Chlorinated naphthalenes have been used in a variety of industries, usually as mixtures. Chronic toxicity varies with the degree of chlorination, with the more highly chlorinated species being more toxic. The clinical signs of toxicity in humans are damage to liver, heart, pancreas, gall bladder, lungs, adrenal glands, and kidney. No animal or human studies have been presented on the carcinogenicity, mutagenicity, or teratogenicity of polychlorinated naphthalenes.

Very little data on aquatic toxicity are available for individual chlorinated naphthalenes. 48-Hour and 96-hour LC_{50} values of octachloronaphthalene over 500,000 µg/l have been reported for Daphnia magna and the bluegill, respectively. A freshwater alga also resulted in a 96-hour LC_{50} value for octachloronaphthalene of over 500,000 µg/l.

Toxicity studies with aquatic organisms are confined to tests with 1-chloronaphthalene on one freshwater fish and two algal species (one fresh and one saltwater). All tests have reported 96-hour LC_{50} values of between 320 and 2,270 µg/l. Exposure of sheepshead minnow to 1-chloronaphthalene in an embryo-larval study resulted in a chronic value of 328 µg/l.

CHLORINATED NAPTHALENES

I. INTRODUCTION

This profile is based on the draft Ambient Water Quality Criteria Document for Chlorinated Naphthalenes (U.S. EPA, 1979).

Chlorinated naphthalenes consist of two fused six carbon-membered aromatic rings where any or all of the eight hydrogen atoms can be replaced with chlorine. The physical properties of the chlorinated naphthalenes are generally dependent on the degree of chlorination. Melting points range from 17°C for 1-chloronaphthalene to 198°C for 1,2,3,4-tetrachloronaphthalene. As the degree of chlorination increases, the specific gravity, boiling point, fire and flash points all increase, while the vapor pressure and water solubility decrease. Chlorinated naphthalenes have been used as the paper impregnant in automobile capacitors (mixtures of tri- and tetrachloronaphthalenes), and as oil additives for engine cleaning, and in fabric dyeing (mixtures of mono- and dichloronaphthalenes). In 1956, the total U.S. production of chlorinated naphthalenes was approximately 3,175 metric tons (Hardie, 1964).

II. EXPOSURE

A. Water

To date, polychlorinated naphthalenes have not been identified in drinking waters (U.S. EPA, 1979). However, these compounds have been found in waters or sediments adjacent to point sources or areas of heavy polychlorinated biphenyl contamination.

B. Food

Polychlorinated naphthalenes appear to be biomagnified in the aquatic ecosystem, with the degree of biomagnification being greater for the more highly chlorinated polychlorinated compounds (Walsh, et al. 1977).

Erickson, et al. (1978) also noted a higher relative biomagnification of the lowest chlorinated naphthalenes by the fruit of apple trees grown on contaminated soil. The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for Halowax 1014 (a mixture of chlorinated naphthalenes) to be 4,800 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on measured non-steady-state bioconcentration studies in brown shrimp.

C. Inhalation

Erickson, et al. (1978) found ambient air concentrations of polychlorinated naphthalenes ranging from 0.025 to 2.90 $\mu g/m^3$ near a polychlorinated naphthalene plant. Concentrations of trichloronaphthalene were as high as 0.95 $\mu g/m^3$, while hexachloronaphthalene concentrations never exceeded 0.007 $\mu g/m^3$.

III. PHARMACOKINETICS

A. Absorption

Pertinent data could not be located in the available literature.

B. Distribution

In the rat fed 1,2-dichloronaphthalene, the chemical and its metabolites were found primarily in the intestine, kidney, and adipose tissue (Chu, et al. 1977).

C. Metabolism

There appears to be appreciable metabolism in mammals of polychlorinated naphthalenes containing four chlorine atoms or less (U.S. EPA, 1979). Cornish and Block (1958) investigated the excretion of polychlorinated naphthalenes in rabbits and found 79 percent of 1-chloronaphthalene, 93 percent of dichloronaphthalene, and 45 percent of tetrachloronaphthalene

were excreted in the urine as metabolites of the parent compounds. Metabolism may involve hydroxylation alone or hydroxylation in combination with dechlorination. In some cases, an arene oxide intermediate may be formed (Ruzo, et al. 1976).

D. Excretion

In rats fed 1,2-dichloronaphthalene, initially more of the chemical and its metabolites were found in the urine; however, by the end of seven days a greater proportion had been excreted in the feces (Chu, et al. 1977). In the first 24 hours, 62 percent of the dose was excreted in the bile, as compared to 18.9 percent lost in the feces. This suggests that there is an appreciable reabsorption and enterohepatic recirculation of this particular chlorinated naphthalene.

IV. EFFECTS

No animal or human studies have been reported on the carcinogenicity, mutagenicity, or teratogenicity of chlorinated naphthalenes. No other reproductive effects were found in the available literature.

A. Chronic Toxicity

Chronic dermal exposure to penta- and hexachlorinated naphthalenes causes a form of chloracne which, if persistent, can progress to form a cyst or sterile abcess (Jones, 1941; Shelley and Kligman, 1957; Kleinfeld, et al. 1972). Workers exposed to these two isomers complained of eye irritation, headaches, fatigue, vertigo, nausea, loss of appetite, and weight loss (Kleinfeld, et al. 1972). More severe exposure to the fumes of polychlorinated naphthalenes has produced severe liver damage, together with damage to the heart, pancreas, gall bladder, lungs, adrenal glands, and kidney tubules (Greenburg, et al. 1939). Chronic toxicity in animals appears to be qualitatively the same (U.S. EPA, 1979). Polychlorinated naphthalenes containing

three or fewer chlorine atoms were found to be nontoxic, while tetrachloronaphthalene resulted in mild liver disease at levels as high as 0.7 mg/kg/-day; the higher chlorinated naphthalenes produce more severe disease at lower doses (Bell, 1953). Because of their insolubility, hepta- and octachloronaphthalene were less toxic when given in suspension than when given in solution.

B. Other Relevant Information

Drinker, et al. (1937) showed enhancement of hepatoxicity of a mixture of ethanol/carbon tetrachloride in rats pretreated with 1.16 mg/m^3 of a penta-/hexachloronaphthalene mixture in air for six weeks. In a similar study trichloronaphthalene was inactive.

V. AQUATIC TOXICITY

A. Acute Toxicity

The 96-hour LC_{50} value reported for the bluegill, Lepomis macrochirus, exposed to 1-chloronaphthalene is 2,270 µg/l (U.S. EPA, 1978). With saltwater species, exposure of the sheepshead minnow, Cyprinodon variegatus, and mysid shrimp, Mysidopsis bahia, to 1-chloronaphthalene provided 96-hour LC_{50} values of 1,290 and 370 µg/l, respectively. Daphnia magna and the bluegill, Lepomis macrochirus, have a slight sensitivity to octachloronaphthalene, with respective 48-hour and 96-hour LC_{50} values greater than 530,000 µg/l (U.S. EPA, 1978).

B. Chronic Toxicity

In the only chronic study reported (embryo-larval), exposure of 1-chloronaphthalene to the sheepshead minnow resulted in a chronic value of 329 µg/l (U.S. EPA, 1978).

C. Plant Effects

A freshwater alga, Selenastrum capricornutum, and a saltwater alga, Skeletonema costatum, when exposed to 1-chloronaphthalene, both produced 96-hour EC_{50} values ranging from 1,000 to 1,300 µg/l based on cell numbers.

Octachloronaphthalene exposure to Selenastrum capricornutum resulted in a 96-hour EC_{50} value of over 500,000 µg/l based on cell numbers (U.S. EPA, 1978).

D. Residues

Pertinent data could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The only standards for polychlorinated naphthalenes are the ACGIH Threshold Limit Values (TLV) adopted by the Occupational Safety and Health Administration and are as follow:

	ACGIH (1977) Threshold Limit Values	
Trichloronaphthalene	5	mg/m^3
Tetrachloronaphthalene	2	mg/m^3
Pentachloronaphthalene	0.5	mg/m^3
Hexachloronaphthalene	0.2	mg/m^3
Octachloronaphthalene	0.1	mg/m^3

There are no state or federal water quality or ambient air quality standards for chlorinated naphthalenes.

The U.S. EPA is presently evaluating the available data and has recommended that a single acceptable daily intake (ADI) of 70 µg/man/day be used for the tri-, tetra-, penta-, hexa-, and octa-chlorinated naphthalenes. This ADI will be used to derive the human health criteria for the chlorinated naphthalenes.

B. Aquatic

For 1-chloronaphthalene, the draft criterion to protect freshwater aquatic life is 29 µg/l as a 24-hour average, not to exceed 67 µg/l at any time. For saltwater aquatic species, the draft criteron is 2.8 µg/l as a 24-hour average, not to exceed 6.4 µg/l at any time (U.S. EPA, 1979).

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LB:46

No. 39

Chlorinated Phenols

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D. C. 20460

October 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

This document discusses the health and environmental effects of some of the di, tri, and tetra-substituted chlorinated phenols. The health effects of p-chloro-m-cresol, 2-chlorophenol, 2,4- and 2,6-dichlorophenol, 2,4,6-trichlorophenol, and pentachlorophenol are discussed in HEBD's nos. 43, 50, 75, 76, 143, and 168, respectively. The National Cancer Institute (1979) recently published the results of a bioassay indicating that 2,4,6-trichlorophenol induces cancer in rats and mice.

CHLORINATED PHENOLS

SUMMARY

Mammalian data supporting chronic effects for most of these compounds is limited. Except for trichlorophenol, there are not sufficient data to indicate whether any of the other chlorinated phenols are carcinogens. In skin painting studies, 3-chlorophenol and 2,4,5-trichlorophenol promoted papillomas. Tetrachlorophenol was not teratogenic or embryolethal in animals, but showed questionable fetotoxic effects. Chronic exposure to 4-chlorophenol produced myoneural disorders in humans and animals. Adverse health effects have been noted in workers exposed to 2,4,5-trichlorophenol. Workers chronically exposed to tetrachlorophenol and pentachlorophenol, perhaps contaminated with small amounts of chlorodibenzodioxins, developed severe skin irritations, respiratory difficulties, and headaches.

Chlorophenols are uncouplers of oxidative phosphorylation, and affect carbohydrate metabolism. Several affect the nervous system, causing convulsions.

The tainting of rainbow trout flesh has been demonstrated at exposures of 15 to 84 ug/l for several of the chlorinated phenols.

I. INTRODUCTION

This profile is based in part on the Ambient Water Quality Criteria Document for Chlorinated Phenols (U.S. EPA, 1980).

The chlorinated phenols represent a group of commercially produced substituted phenols and cresols also referred to as chlorophenols or chlorocresols. The compounds p-chloro-m-cresol, 2,4- and 2,6-dichlorophenols, 2,4,6-trichlorophenol, and pentachlorophenol are discussed in separate hazard profiles.

Purified chlorinated phenols are colorless, crystalline solids (with the exception of 2-chlorophenol which is a liquid), while the technical grades may be light tan or slightly pink due to impurities. Chlorophenols have pungent odors. In general, the volatility of chlorinated phenols decreases and the melting and boiling points increase as the number of substituted chlorine atoms increases. Although the solubility of chlorinated phenols in aqueous solutions is relatively low, it increases markedly when the pH of the solution exceeds their specific pKa. The solubilities of chlorinated phenols and chlorocresols (with the exception of 2,4,6-trichloro-m-cresol) range from soluble to very soluble in relatively non-polar solvents such as benzene and petroleum ether (U.S. EPA, 1980).

The chlorinated phenols that are most important commercially are 4-chlorophenol, 2,4,-dichlorophenol, 2,4,5-trichlorophenol, 2,3,4-tetrachlorophenol, pentachlorophenol, and 4-chloro-o-cresol. Many of the chlorophenols have no commercial application but are

produced to some extent as byproducts of the commercially important compounds. The highly toxic polychlorinated dibenzo-p-dioxins may be formed during the chemical synthesis of some chlorophenols. During the chlorination of drinking waters and wastewater effluents, chlorophenols may be inadvertently produced (U.S. EPA, 1980).

Chlorinated phenols are used as intermediates in the synthesis of dyes, pigments, phenolic resins, pesticides, and herbicides. Certain chlorophenols are used directly as flea repellants, fungicides, wood preservatives, mold inhibitors, antiseptics, disinfectants, and antigumming agents for gasoline.

Chlorinated phenols undergo photolysis in aqueous solutions as a result of ultraviolet irradiation; photodegration leads to the substitution of hydroxyl groups in place of the chlorine atoms with subsequent polymerization (U.S. EPA, 1980). Microbial degradation of chlorophenols has been reported by numerous investigators (U.S. EPA, 1980).

3-CHLOROPHENOL and 4-CHLOROPHENOL

II. EXPOSURE

Monochlorophenols have been found in surface waters in the Netherlands at concentrations of 2 to 20 ug/l (Piet and DeGrunt, 1975). Ingestion of chlorobenzene can give rise to internal exposure to 2-, 3-, and 4-chlorophenols, as chlorobenzene is metabolized to monochlorophenols (Lindsay-Smith, et al. 1972). No data were found demonstrating the presence of monochlorophenol in food.

For 4-chlorophenol the U.S. EPA has estimated the weighted average bioconcentration factor for the edible portions of all aquatic organisms consumed by Americans to be 12. This estimate is base don the octanol/water partition coefficient.

Data were not found in the available literature regarding inhalation exposure.

III. PHARMACOKINETICS

Systematic studies of the pharmacokinetics of 3- or 4-chlorophenol are not available. Dogs excreted 87 percent of administered 4-chlorophenol in the urine as sulfuric and glucuronic conjugates (Karpow, 1893, as cited in U.S. EPA, 1980).

IV. EFFECTS

A. Carcinogenicity

Information is not adequate to determine whether 3- or 4-chlorophenol posses carcinogenic properties. A 20 percent solution of 3-chlorophenol promoted papillomas when repeatedly applied to the backs of mice after initiation with dimethylbenzanthrene (Boutwell and Bosch, 1959).

B. Mutagenicity, Teratogenicity and Other Reproductive Effects

Pertinent data cannot be located in the available literature regarding mutagenicity, teratogenicity and other reproductive effects.

C. Chronic Toxicity

Rats exposed 6 hrs/day for four months to 2 mg 4-chlorophenol/m^3 showed a temporary weight loss and increased myoneural

excitability. Body temperature and hematological parameters were not altered (Gurova, 1964). Workers exposed to 4-chlorophenol had a significantly higher incidence of neurological disorders when compared with unexposed workers in the same plant. Peripheral nerve stimulation studies showed increased myoneural excitability in exposed workers. The minimum detection distance in a two-point touch discrimination test was also increased (Gurova, 1964).

D. Other Relevant Information

3- and 4-Chlorophenol are weak uncouplers of oxidative phosphorylation (U.S. EPA, 1980).

2,5-DICHLOROPHENOL, 3,4-DICHLOROPHENOL, and 3,5-DICHLOROPHENOL

II. EXPOSURE

Unspecified dichlorophenol (DCP) isomers have been detected in concentrations of 0.01 to 1.5 ug/l in Dutch surface waters (Piet and DeGrunt, 1975). Dichlorophenols have been found in flue gas condensates from municipal incinerators (Olie, et al., 1977). No data on exposure from foods or the dermal route were found. Exposure to other chemicals can result in exposure to dichlorophenols (i.e., dichlorobenzenes, lindane, and the alpha and delta isomers of 1,2,3,4,5,6-hexachlorocyclohexane are metabolized by mammals to dichlorophenols) (Kohle, et al., 1976; Foster and Saha, 1978).

III. PHARMACOKINETICS

Pharmacokinetic data specific to these dichlorophenol isomers

could not be located in the available literature. It is reasonable to assume that the dichlorophenol isomers are absorbed through the skin and from the gut, and rapidly eliminated as are other chlorophenols (U.S. EPA, 1980).

IV EFFECTS

A. Carcinogenicity

Pertinent data cannot be located in the available literature; 2,4-DCP has been selected for bioassay.

B. Mutagenicity

None of the dichlorophenols were found to be mutagenic in the Ames test with or without microsomal activation (Rasanen and Hattula, 1977). Mutagenicity in mammalian test systems has not been studied (U.S. EPA, 1980).

C. Teratogenicity, Other Reproductive Effects and Chronic Toxicity

Pertinent data cannot be located in the available literature regarding teratogenicity, other reproductive effects and chronic toxicity.

D. Other Relevant Information

Phenol, and the lower chlorinated phenols, including 2,6-dichlorophenol are convulsants (Farquharson, et al, 1958); the latter readily penetrates the bovine lens capsule (Ismail et al., 1976), and inhibits oxidative phosphorylation in that tissue (Korte et al., 1976). The significance of these results is as yet unknown.

TRICHLOROPHENOLS*

I. EXPOSURE

Trichlorophenols have been detected in surface waters in Holland at concentrations ranging from 0.003 to 0.1 ug/l (Piet and DeGrunt, 1975). 2,4,5-Trichlorophenol can be formed from the chlorination of phenol in water (Burttschell et al., 1959).

One possible source of trichlorophenol exposure for humans is through the food chain, as a result of the metabolism by grazing animals of ingested chlorophenoxy acid herbicides 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) and Silvex (2-(2,4,5-trichlorophenoxy)-propionic acid). Residues of these herbicides on sprayed forage are estimated to be 100-300 ppm. Studies in which cattle and sheep were fed these herbicides at 300, 1000, and 2000 ppm (Clark et al., 1976) showed the presence of 2,4,5-trichlorophenol in various tissues. In lactating cows fed 2,4,5-T at 100 ppm, an occasional residue of 0.06 ppm or less of trichlorophenol was detected in milk (Bjerke et al., 1972).

Exposure to other chemicals such as trichlorobenzenes, lindane, the alpha and delta isomers of 1,2,3,4,5,6- hexachlorocyclohexane, isomers of benzene hexachloride, and the insecticide Ronnel can result in exposure to trichlorophenols via metabolic degradation of the parent compound (U.S. EPA, 1980).

*The health and environmental effects of 2,4,6-trichlorophenol are more extensively discussed in HEBD No. 168.

The U.S. EPA (1980) has estimated the weighted average bioconcentration factors for the edible portions of all aquatic organisms consumed by Americans to be 130 to 2,4,5-trichlorophenol and 110 for 2,4,6-trichlorophenol. These estimates are based on the octanol/water partition coefficients for these chemicals.

Trichlorophenols are found in flue gas condensates from municipal incinerators (Olie et al., 1977).

Most commercial trichlorophenols and their derivatives contain appreciable amounts of the contaminant 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and/or its homologues (U.S. EPA, 1980). The presence of this highly toxic contaminant caused the U.S. EPA to publish a Rebuttable Presumption Against Registration (RPAR) and Continued Registration of Pesticide Products Containing 2,4,5-T (43 FR 17116). The published RPAR indicated that 2,4,5-trichlorophenol is also the subject of a separate potential RPAR.

III. PHARMACOKINETICS

A. Absorption and Distribution

The oral LD_{50} in the rat has been variously reported as 820 and 2960 mg/kg (U.S. EPA 1980). Information dealing with tissue distribution after administration of trichlorophenols could not be located in the available literature. Feeding of 2,4,5-T and Silvex to sheep and cattle produced high levels of 2,4,5-trichlorophenol in liver and kidney and low levels in muscle and fat (Clark et al., 1976).

B. Metabolism

Pertinent data could not be located in the available literature.

C. Excretion

In rats, 82 percent of an administered dose (1 ppm in the diet for 3 days) of 2,4,6-trichlorophenol was eliminated in the urine and 22 percent in the feces. Radiolabeled feces was not detected in liver, lung or fat obtained 5 days after the last dose (Korte, et al., 1976). The approximate blood half-life for 2,4,5-trichlorophenol is 20 hours, after dosing of sheep with Erbon (an herbicide which is metabolized to 2,4,5-trichlorophenol) (Wright et al., 1970).

2,4,5-Trichlorophenol was detected in 1.7 percent of urine samples collected from the general population (Kutz et al., 1978).

IV. EFFECTS

A. Carcinogenicity

A 21 percent solution of 2,4,5-trichlorophenol in acetone promoted papillomas but not carcinomas in mice after initiation with dimethylbenzanthrene (Boutwell and Bosch, 1959). 2,3,5-, 2,3,6-, 2,4,5-, and 2,4,6-Trichlorophenol were not found to be mutagenic in the Ames test with and without microsomal activation (Rasanen and Hattula, 1977). 2,4,6-Trichlorophenol induces cancer in rats and mice (NCI, 1979).

C. Teratogenicity and Other Reproductive Effects

Pertinent data could not be located in the available literature regarding teratogenicity and other reproductive effects.

D. Chronic Toxicity

When rats were fed 2,4,5-trichlorophenol (99 percent pure) for 98 days (McCollister et al., 1961), levels of 1000 mg trichlorophenol/kg feed (assumed to be equivalent to 100 mg/kg body weight) or less produced no adverse effects as judged by behavior, mortality, food consumption, growth, terminal hematology, body and organ weights, and gross or microscopic pathology. At 10,000 mg/kg diet (1000 mg/kg body weight), growth was slowed in females. Histopathologic changes were noted in liver and kidney. There were no hematologic changes. At 3000 mg/kg feed (300 mg/kg body weight), milder histopathologic changes in liver and kidney were observed. The histopathologic changes were considered to be reversible.

Adverse health effects including chloracne, porphyria cutanea-tarda with hyperpigmentation, hirsutism and urinary excretion of porphyrins were described in workers involved in the manufacture of 2,4,5-D and 2,4,5-T (Bleiberg, et al., 1964). It is possible that some of these symptoms represent 2,3,7,8-tetrachlorodibenzo-p-dioxin toxicosis (U.S. EPA, 1980).

E. Other Relevant Information

Studies on the subcellular effects of trichlorophenols shows them to be powerful uncouplers of oxidative phosphorylation. 2,4,5-Trichlorophenol readily penetrates the bovine eye lens (Ismael, 1975), and affects the carbohydrate metabolizing system of that tissue (Korte et al., 1976).

II. EXPOSURE

There are three isomers of tetrachlorophenol: 2,3,4,5-, 2,3,5,6, and, most importantly, 2,3,4,6-tetrachlorophenol. Commercial pentachlorophenol contains 3 to 10 percent tetrachlorophenol (Goldstein et al., 1977; Schwetz et al., 1974). Commercial tetrachlorophenol contains pentachlorophenol (27 percent) and toxic nonphenolic impurities such as chlorodibenzofurans and chlorodioxin isomers (Schwetz et al., 1974). The presence of tetrachlorophenol in drinking water has not been documented (U.S. EPA, 1980). Exposure to other chemicals such as tetrachlorobenzenes can result in exposure to tetrachlorophenols via degradation of the parent compound (Kohli et al., 1976).

Data could not be located in the available literature on ingestion from foods. The U.S. EPA (1980) has estimated a weighted average bioconcentration factor for 2,3,4,6-tetrachlorophenol of 320 for the edible portion of aquatic organisms consumed by Americans. This estimate is based on the octanol/water partition coefficient of 2,3,4,5-tetrachlorophenol.

Tetrachlorophenols have been found in flue gas condensates from municipal incinerators (Olie et al., 1977).

II. PHARMACOKINETICS

A. Absorption and Distribution

Pertinent data could not be located in the available literature regarding absorption and distribution.

B. Metabolism and Excretion

In rats, over 98 percent of an intraperitoneally administered dose of 2,3,4,6-tetrachlorophenol was recovered in the urine in 24 hours. About 66 percent was excreted as the unchanged compound and 35 percent as tetrachloro-p-hydroquinone. About 94 percent of the intraperitoneal dose of 2,3,4,6-tetrachlorophenol was recovered in the urine in 24 hours, primarily as the unchanged compound with trace amounts of trichloro-p-hydroquinone. Fifty-one percent of the intraperitoneal dose of 2,3,4,5-tetrachlorophenol was recovered in the urine in 24 hours, followed by an additional 7 percent in the second 24 hours, primarily as the unchanged compound with trace amounts of trichloro-p-hydroquinone. In these experiments, the urine was boiled to split any conjugates (Alhborg and Larsson, 1978).

Fungi methylate pentachlorophenols to the corresponding anisoles, (U.S. EPA, 1980). The chronic health effects consequences of these compounds are not known, and the possibility of methylation in mammalian liver or intestine has not been documented.

A. Carcinogenicity

Pertinent data could not be located in the available literature.

B. Mutagenicity

2,3,4,6-Tetrachlorophenol was reported to be nonmutagenic in the Ames test, both with and without microsomal activation (Rasanen et al., 1977).

C. Teratogenicity

Tetrachlorophenol did not induce teratogenic effects in rats at doses of 10 or 30 mg/kg administered on days six through 15 of gestation (Schwetz et al., 1974).

D. Other Reproductive Effects

Tetrachlorophenol produced fetotoxic effects (subcutaneous edema and delayed ossification of skull bones) in rats at doses of 10 and 30 mg/kg administered on days six through 15 of gestation (Schwetz, et al., 1974).

E. Chronic Toxicity

Sawmill workers exposed to wood dust containing 100-800 ppm 2,3,4,6-tetrachlorophenol, 30-40 ppm pentachlorophenol, 10-50 ppm chlorophenoxyphenols, 1-10 ppm chlorodibenzofurans and less than 0.5 ppm chlorodibenzo-p-dioxins developed severe skin irritations, respiratory difficulties and headaches (Levin et al., 1976).

No toxicity studies of 90 days or longer were found in the available literature.

F. Other Relevant Information

2,3,4,6-Tetrachlorophenol is a strong uncoupler of oxidative phosphorylation, and affects mixed function oxidases (U.S. EPA, 1980).

CHLORINATED PHENOLS

I. AQUATIC TOXICITY

A. Acute Toxicity (U.S. EPA, 1980)

The acute toxicity of eight chlorophenols was determined

in nine bioassays. Acute 96-hour LC_{50} values for freshwater fish ranged from 30 ug/l for the fathead minnow, Pimephales promelas, for 4-chloro-3-methylphenol to 9,040 ug/l for the fathead minnow for 2,4,6-trichlorophenol. Among the freshwater invertebrates, toxicity for Daphnia magna was tested with seven chlorophenols in eight 48-hour static bioassays. Acute LD_{50} values ranged from 290 ug/l for 2,3,4,6-tetrachlorophenol and 4-chloro-2-methylphenol to 6,040 ug/l for 2,4,6-trichlorophenol. Acute 96-hour static LC_{50} values in the sheepshead minnow ranged from 1,660 ug/l for 2,4,5-trichlorophenol to 5,350 ug/l for 4-chlorophenol. The only marine invertebrate species acutely tested has been the mysid shrimp, Mysidopsis bahia, with acute 96-hour static LC_{50} values reported as: 3,830 ug/l for 2,4,5-trichlorophenol; 21,900 ug/l for 2,3,5,6-tetrachlorophenol, and 29,700 ug/l for 4-chlorophenol.

B. Chronic Toxicity (U.S. EPA, 1980)

No data other than that presented in the specific hazard profile for 2-chlorophenol, 2,4-dichlorophenol, and pentachlorophenol were available for freshwater organisms. An embryo-larval study provided a chronic value of 180 ug/l for sheepshead minnows, Cyprinodon variegatus, exposed to 2,4-dichloro-6-methylphenol.

C. Effects on Plants (U.S. EPA, 1980)

Effective concentrations for 15 tests on four species of

freshwater plants ranged from chlorosis LC_{50} of 603 ug/l for 2,3,4,6-tetrachlorophenol to 598,584 ug/l for 2-chloro-6-methylphenol in the duckweed, Lemna minor. The marine algae, Skeletonema costatum, has been used to assess the relative toxicities of three chlorinated phenols. Effective concentrations, based on chlorophyll a content and cell growth, of 440 and 500 ug/l were obtained for 2,3,5,6-tetrachlorophenol. 2,4,5-Trichlorophenol and 4-chlorophenol were roughly two and seven times as potent, respectively, as 2,3,5,6-tetrachlorophenol.

D. Residues

Steady-state bioconcentration factors have not been calculated for the chlorinated phenols. However, based upon octanol/water partition coefficients, the following bioconcentration factors have been estimated for aquatic organisms with a lipid content of eight percent: 41 for 4-chlorophenol; 440 for 2,4,5-trichlorophenol; 380 for 2,4,6-trichlorophenol; 1,100 for 2,3,4,6-tetrachlorophenol; and 470 for 4-chloro-3-methylphenol (U.S. EPA, 1980).

E. Miscellaneous

The tainting of fish flesh by exposure of rainbow trout, Salmo gairdneri, to various chlorinated phenols has derived a range of estimated concentrations not impairing the flavor of cooked fish from 15 ug/l for 2-chlorophenol to 84 ug/l for 2,3-dichlorophenol (U.S. EPA, 1980).

II. EXISTING GUIDELINES AND STANDARDS

Water quality criteria recommended for chlorinated phenols by the U.S. EPA (1980) are given in the following table:

Recommended Water Quality Criteria

Compound	Human Health: Criterion from Organoleptic Effects (ug/l)	Human Health: Criterion from Toxicological Data (ug/l)	Aquatic Life (ug/l)
Monochlorophenols			
3-chlorophenol	0.1	none	29,700(b)
4-chlorophenol	0.1	none	
Dichlorophenols			
2,3-dichlorophenol	0.4	none	
2,4-dichlorophenol	0.3	3.09	365(a)
2,5-dichlorophenol	0.5	none	
2,6-dichlorophenol	0.2	none	
3,4-dichlorophenol	0.3	none	
Trichlorophenols			
2,4,5-trichlorophenol	1.0	1600	970(a)
2,4,6-trichlorophenol	2.0	12(c)	
Tetrachlorophenols			
2,3,4,6-tetrachlorophenol	1	none	440(b)
2,3,5,6-tetrachlorophenol			

(a) Chronic toxicity value, freshwater

(b) Acute toxicity value, saltwater

(c) Based on NCI carcinogenesis bioassay

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No. 40

Chloroacetaldehyde

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

CHLOROACETALDEHYDE

Summary

No carcinogenic effects were observed in female ICR Ha Swiss mice following administration of chloroacetaldehyde via dermal application or subcutaneous injection. Mutagenic effects, varying from weak to strong, have been reported in the yeasts Schizosaccharomyces pombe and Saccharomyces cerivisiae and in certain Salmonella bacterial tester strains. There is no evidence in the available literature to indicate that chloroacetaldehyde produces teratogeric effects. Occupational exposure studies have shown chloroacetaldehyde to be a severe irritant of the eyes, mucous membranes and skin.

Data concerning the effects of chloroacetaldehyde on aquatic organisms were not found in the available literature.

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CHLOROACETALDEHYDE

I. INTRODUCTION

Chloroacetaldehyde (C_2H_3ClO) is a clear, colorless liquid with a pungent odor. Its physical properties include: boiling point, 90.0-100.1°C (40 percent sol.); freezing point, -16.3°C (40 percent sol.); and vapor pressure, 100 mm at 45°C (40 percent sol.). Synonyms for chloroacetaldehyde are: monochloroacetaldehyde, 2-chloroacetaldehyde and chlorocldehyde. It is soluable in water, acetone and methanol. Primary uses of chloroacetaldehyde include: use as a fungicide, use in the manufacture of 2-aminothiazole, and use in the removal of bark from tree trunks.

II. EXPOSURE

No monitoring data are available to indicate ambient air or water levels of chloroacetaldehyde, nor is any information available on possible exposure from food.

Occupational routes of human exposure to chloroacetaldehyde are primarily through inhalation and skin absorption.

Bioaccumulation data on chloroacetaldehyde were not found in the available literature. However, 2-chloroacetaldehyde is known to be a chemically reactive compound and its half-life in aqueous solution has been reported as slightly greater than 24 hours (Van Duuren et al., 1972).

III. PHARMACOKINETICS

A. Absorption

Exposure to chloroacetaldehyde is primarily through inhalation and skin absorption.

Chloroacetaldehyde proved to be very lethal by inhalation. In an inhalation study conducted by Lawrence et al. (1972), mice were placed in a chloroacetaldehyde-free chamber and air containing chloroacetaldehyde vapor was then passed

through the chamber. The time of exposure required to kill 50% of the animals, LT_{50}, was 2.57 min. (the chamber atmosphere was calculated to have reached 45% equilibrium within that time.)

In comparison studies conducted on chloroacetaldehyde and 2-chloroethanol, chloroacetaldehyde was reported as exhibiting greater irritant activity, but having lesser penetrant capacity (Lawrence et al., 1972).

B. Distribution

Information on the distribution of chloroacetaldehyde was not found in the available literature.

C. Metabolism

Chloroacetaldehyde appears to be a metabolite of a number of compounds including 1,2-dichloroethane, chloroethanol and vinyl chloride (McCann et al., 1975).

Johnson (1967) conducted in vitro studies on rat livers, the results of which indicated that S-carboxymethylglutathione was probably formed via chloroacetaldehyde metabolic action. Based upon these studies, Johnson suggested that the same metabolic mechanism was operative in the in vivo conversion of chloroethanol to S-carboxymethylglutathione.

In recent studies, Watanabe et al. (1976a,b) reported that chloroacetaldehyde would conjugate with glutathione and cysteine leading ultimately to the types of urinary metabolites found in animals exposed to vinyl chloride. The authors reported that as nonprotein free sulfhydral concentrations are depleted, the alkylating metabolites, one of which is chloroacetaldehyde, are likely to react with protein, DNA and RNA, eliciting proportionally greater toxicity. This is in agreement with other studies conducted on vinyl chloride metabolism (Hefner et al., 1975; Bolt et al., 1977).

Chloroacetaldehyde was shown to cause the destruction of lung hemoprotein, cytochrome P450, as well as liver microsomal cytochrome P450, with no requirement for NADPH (Harper and Patel, 1978). The results suggested that the aldehydes tested, one of which was chloroacetaldehyde, were the toxic intermediates which inactivated pulmonary enzymes following exposure to some environmental agents.

D. Excretion

Information specifically on the rates and routes of chloroacetaldehyde elimination was not found in the available literature. Studies on vinyl chloride and ethylene dichloride, however, indicate that chloroacetaldehyde, as an intermediate metabolite, may ultimately convert to a number of urinary metabolites--including chloroacetic acid, S-carboxymethylcysteine and thiodiacetic acid--depending on the particular metabolic pathway involved in the biotransformation of the parent compound (Johnson, 1967; Yllner, 1971; Watanabe, 1976a,b).

IV. EFFECTS

A. Carcinogenicity

In a study on the carcinogenic activity of alkylating agents, Van Duuren et al. (1974) exposed female ICR Ha Swiss mice to 2-chloroacetaldehyde (assayed as diethylacetal). The routes of administration were via skin and subcutaneous injection. The authors reported no significant tumor induction. Later studies confirmed these findings (Goldschmidt, personal communication, 1977). However, in a report by McCann et al. (1975), the authors stated that previous reports of changes of respiratory epithelium in lungs of rats exposed to chloroacetaldehyde were suggestive of premalignant conditions.

B. Mutagenicity

Many studies have been reported which show that chloroacetaldehyde exhibits varying degrees of mutagenic activity (Huberman et al., 1975; Border

and Webster, 1976; Elmore et al., 1976; Rosenkranz, 1977). Loprieno et al. (1977) reported that 2-chloroacetaldehyde showed only feeble genetic activity when tested in the yeasts Schizosaccharomyces pombe and Saccharomyces cerevisiae. However, McCann et al. (1975) reported that chloroacetaldehyde was quite effective in reverting Salmonella bacterial tester strain TA 100, but did not revert TA 1535. In a later study, Rosenkranz (1977) found that 2-chloroacetaldehyde did display some mutagenic activity towards TA 1535.

In a study conducted by Elmore et al. (1976) the authors reported that the chloroacetaldehyde monomer and monomer hydrate were more mutagenically active that the dimer hydrate and the trimer.

Rannug et al. (1976) reported that the mutagenic effectiveness of chloroacetaldehyde is about 10^4 times higher than expected from kinetic data.

C. Teratogenicity and Other Reproductive Effects

Pertinent information could not be found in the available literature.

D. Chronic Toxicity

No chronic information could be found in the available literature. However, extensive toxicity studies conducted by Lawrence et al. (1972) revealed some subacute effects of chloroacetaldehyde on Sprague-Dawley and Black Bethesda rats. Groups of rats received .001879 and .003758 ml/kg of chloroacetaldehyde (representing 0.3 and 0.6 of the acute LD_{50} dose, respectively) daily for 30 consecutive days. Hematologic tests at the end of 30 days showed that there was a significant decrease in hemoglobin, hematocrit, and erthrocytes in the high dose group; the low dose group showed an increase in monocytes accompanied by a decrease in lymphocytes. The animals were sacrificed and organ-to-body weight ratios were calculated. Ratios for both brain and lungs were significantly greater in the low dose group, while the high dose group showed a significant increase in the brain, gonads, heart, kidneys, liver, lungs and spleen.

Histological examination did not reveal any abnormalities attributable to chloroacetaldehyde except for the lungs which showed more severe bronchitis, bronchiolitis and bronchopneumonia than were seen in controls.

In another subacute (subchronic) study, chloroacetaldehyde was administered to rats in doses of .00032, .00080, .00160 and .00320 ml/kg, three times a week for 12 weeks. Hematologic determinations showed no significant differences between controls and the two lower dose groups, while animals administered .0016 ml/kg showed a decrease in red cell count and lymphocytes and an increase in segmented neutrophiles; the highest dose group showed a significant decrease in red blood cells and hemoglobin with an increase in clotting time and segmented neutrophiles. Organ-to-body weight ratios were determined for several organs and, although there were some significant differences from controls, there were no apparent dose-related responses.

D. Acute Toxicity

Lawrence et al. (1972) conducted a series of acute toxicity tests on ICR mice, Sprague-Dawley and Black Bethesda rats, New Zealand albino rabbits and Hartlez strain guinea pigs. The results were reported as follows: the LD_{50}s (ml/kg) for chloroacetaldehyde administered intraperitoneally ranged from .00598 in mice to .00464 in rabbits; the LD_{50}s (ml/kg) for chloroacetaldehyde administered intragastrically were reported as .06918 in male mice, .07507 in female rats and .08665 in male rats; the dermal LD_{50} (ml/kg) in rabbits was reported as .2243; and the inhalation LT_{50} in mice was reported as 2.57 min.

E. Other Relevent Information

Case studies show that contact with a strong solution of chloroacetaldehyde in the human eye will likely result in permanent impairment of vision and skin contact with a potent solution will result in burns (Proctor and Hughes, 1978).

V. AQUATIC TOXICITY

Data concerning the effects of chloroacetaldehyde on aquatic organisms were not found in the available literature.

VI. EXISTING GUIDELINES

The 8-hour, TWA occupational exposure limit established for chloroacetaldehyde is 1 ppm. This TLV of 1 ppm was set to prevent irritation (ACGIH, 1976).

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No. 41

Chloroalkyl Ethers

Health and Environmental Effects

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WASHINGTON, D.C. 20460

APRIL 30, 1980

41-1

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated chloroalkyl ethers and has found sufficient evidence to indicate that this compound is carcinogenic.

CHLOROALKYL ETHERS

SUMMARY

Bis(chloromethyl)ether (BCME), chloromethyl methyl ether (CMME), and bis(2-chloroethyl)ether (BCEE) have shown carcinogenic effects in animal studies following administration by various routes. Epidemiological studies in the United States, Germany, and Japan have indicated that workers exposed to BCME and CMME developed an increased incidence of respiratory tract tumors.

Testing of BCME, CMME, BCEE, and bis(2-chloroisopropyl)-ether (BCIE) in the Ames Salmonella assay and in E. coli have indicated that these compounds have mutagenic activity. Cytogenetic studies of lymphocytes from workers exposed to BCME and CMME have reported an increased frequency of aberrations, which appear to be reversible.

There is no available evidence to indicate chloroalkyl ethers produce adverse reproductive or teratogenic effects.

The information base for freshwater organisms and chloroalkyl ethers is limited to a few toxicity tests of 2-chloroethyl vinyl ether and bis(2-chloroethyl)ether. The reported 96-hour LC_{50} value for bis(2-chloroethyl)ether in the bluegill is greater than 600,000 µg/l. A "no effect" value of 19,000 µg/l was observed using the fathead minnow in an embryo-larval test. Bis(2-chloroethyl)ether has a reported bioconcentration factor of 11 in a 14-day exposure to bluegills. The half-life is from four to seven days. The reported 96-hour LC_{50} value for the bluegill and 2-chloroethyl vinyl ether is 194,000 µg/l.

CHLOROALKYL ETHERS

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for chloroalkyl ethers (U.S. EPA, 1979).

The chloroalkyl ethers are compounds with a hydrogen atom in one or both of the aliphatic ether chains substituted by a chlorine atom. The chemical reactivity of these compounds varies greatly, depending on the nature of the aliphatic groups and the placement of the chlorine atoms. The most reactive compounds are those with short aliphatic groups and those in which chlorine substitution is closest to the ether oxygen (alpha-chloro) (U.S. EPA, 1979).

As an indication of their high reactivity, chloromethyl methyl ether (CMME), bis(chloromethyl)ether (BCME), 1-chloroethyl ethyl ester, and 1-chloroethyl methyl ether decompose rapidly in water. The beta-chloroethers, bis(2-chloroethyl)-ether (BCEE) and bis(2-chloroisopropyl)ether (BCIE) are more stable in aqueous systems; they are practically insoluble in water but miscible with most organic solvents (U.S. EPA, 1979).

The chloroalkyl ethers have a wide variety of industrial and laboratory uses in organic synthesis, textile treatment, the manufacture of polymers and insecticides, in the preparation of ion exchange resins, and as degreasing agents (U.S. EPA, 1979).

While the short chain alpha-chloroalkyl ethers (BCME,, CMME) are very unstable in aqueous systems, they appear to be relatively stable in the atmosphere (Tou and Kallos, 1974). Bis(chloromethyl)ether will form spontaneously in the pres-

ence of both hydrogen chloride and formaldehyde (Frankel, et al. 1974).

II. EXPOSURE

The beta-chloroalkyl ethers have been monitored in water. Industrial effluents from chemical plants involved in the manufacture of glycol products, rubber, and insecticides may contain high levels of these ethers (U.S. EPA, 1979). The highest concentrations in drinking water of bis(2-chloroethyl)ether, bis(2-chloroisopropyl)ether, and bis-1,2-(2-chloroethoxy)ethane (BCEXE) reported by the U.S. EPA (1975) are 0.5, 1.58, and 0.03 µg/l, respectively. The average concentration of these compounds in drinking water is in the nanogram range (U.S. EPA, 1979). Chloroalkyl ethers have been detected in the atmosphere, and human inhalation exposure appears to be limited to occupational settings.

The chloroalkyl ethers have not been monitored in food (U.S. EPA, 1979). The betachloroalkyl ethers, because of their relative stability and low water solubility, may have a tendency to be bioaccumulated. The U.S. EPA (1979) has estimated the weighted bioconcentration factor to be 25 for the edible portions of fish and shellfish consumed by Americans. This is based on the measured steady-state bioconcentration studies in bluegills. Bioconcentration factors for BCME (31) and BCIE (106) have been derived using a proportionality constant related to octanol/water partition coefficients (U.S. EPA, 1979). Dermal exposure for the chloroalkyl ethers has not been determined (U.S. EPA, 1979).

III. PHARMACOKINETICS

A. Absorption

Experiments with radio-labelled BCIE and BCEE in female rats and monkeys have indicated that both compounds are readily absorbed in the blood following oral administration (Smith, et al., 1977; Lingg, et al., 1978). Pertinent data could not be located in the available literature retrieved on dermal or inhalation absorption of the alkyl ethers.

B. Distribution

Species differences in the distribution of radio-labelled BCIE have been reported by Smith, et al. (1977). Monkeys, as compared to rats, retain higher amounts of radioactivity in the liver, muscle, and brain. Urine and expired air from the rat contained higher levels of radioactivity than those found in the monkey. Blood levels of BCIE in monkeys reached a peak within two hours following oral administration and then declined in a biphasic manner ($t_{1/2}$'s = 5 hours and 2 days for the first and second phases, respectively).

C. Metabolism

The biotransformation of BCEE in rats following oral administration appears to involve cleavage of the ether linkage and subsequent conjugation (Lingg, et al., 1978). Thiodiglycolic acid and chloroethanol-D-glucuronide were identified as urinary metabolites of BCEE. Metabolites of BCIE identified in the rat included 1-chloro-2-propanol, propylene oxide, 2-(1-methyl-2-chloroethoxy)-propionic acid, and carbon dioxide (Smith, et al., 1977).

D. Excretion

BCEE administered orally to rats was excreted rapidly, with more than 60 percent of the compound excreted within 24 hours. Virtually all of this elimination was via the urine (Lingg, et al., 1978).

IV. EFFECTS

A. Carcinogenicity

There are several studies with bis(chloromethyl)-ether (BCME), chloromethyl methyl ether (CMME), and bis(2-chloroethyl)ether (BCEE) that show carcinogenic effects. BCME induced malignant tumors of the male rat respiratory tract following inhalation exposure (Kuschner, et al., 1975). Application of BCME and BCEXE to the skin of mice produced skin tumors (Van Duuren, et al., 1968), while subcutaneous injection of BCME to newborn mice induced pulmonary tumors (Gargus, et al., 1969).

Oral administration of bis(2-chloroethyl)ether (BCEE) to mice has been shown to increase the incidence of hepatocellular carcinomas in males (Innes, et al., 1969).

Epidemiological studies of workers in the United States, Germany, and Japan who were occupationally exposed to BCME and CMME have indicated these compounds are human respiratory carcinogens (U.S. EPA, 1979).

Both BCME and CMME have been shown to accelerate the rate of lung tumor formation in Strain A mice following inhalation exposure (Leong, et al., 1971). BCME and BCEE have shown tumor initiating activity for mouse skin, while CMME showed only weak initiating activity (U.S. EPA, 1979).

Preliminary results of a National Cancer Institute study indicate that oral administration of BCIE does not produce an increase in tumor incidence (U.S. EPA, 1979).

B. Mutagenicity

Testing of the chloroalkyl ethers in the Ames Salmonella assay on E. coli have indicated that BCME, CMME, BCIE, and BCEE all produced mutagenic effects (U.S. EPA, 1979). BCEE has also been reported to induce mutations in Saccharomyces cerevisiae (U.S. EPA, 1979). Neither BCEE nor BCIE showed mutagenic effects in the heritable translocation test in mice (Jorganson, et al. 1977). An increase in cytogenetic aberrations in the lymphocytes of workers exposed to BCME and CMME was reported by Zudova and Landa (1977); the frequency of aberrations decreased following the removal of workers from exposure.

C. Teratogenicity and Other Reproductive Effects

Pertinent data could not be located in the available literature.

D. Chronic Toxicity

Chronic occupational exposure to CMME contaminated with BCME has produced bronchitis in workers (U.S. EPA, 1979). Cigarette smoking has been found to act synergistically with CMME exposure to produce bronchitis (Weiss, 1976, 1977).

Animal studies have indicated that chronic exposure to BCIE produces liver necrosis in mice. Exposure in rats causes major effects on the lungs, including congestion and pneumonia (U.S. EPA, 1979).

E. Other Relevant Information

The initiating activity of several chloroalkyl ethers indicates that these compounds may interact with other agents to produce skin papillomas (Van Duuren, et al., 1969, 1972).

V. AQUATIC TOXICITY

A. Acute Toxicity

The reported static 96-hour LC_{50} value for the bluegill (Lepomis macrochirus) with 2-chloroethyl vinyl ether (concentration unmeasured) is 194,000 µg/l (U.S. EPA, 1978). The 96-hour LC_{50} values for the bluegill could not be determined in a static test for bis(2-chloroethyl)ether with exposure concentrations as high as 600,000 µg/l. The concentration of the ether was not monitored during the bioassay. Pertinent data could not be located in the available literature on saltwater species.

B. Chronic Toxicity

An embryo-larval test was conducted with bis(2-chloroethyl)ether and the fathead minnow, (Pimephales promelas). Adverse effects were not observed at test concentrations as high as 19,000 µg/l.

C. Plant Effects

Pertinent data could not be located in the available literature.

D. Residues

Using bis(2-chloroethyl)ether, a bioconcentration factor of 11 was determined during a 14-day exposure of bluegills (U.S. EPA, 1979). The half-life was observed to be between four and seven days.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria may be changed.

A. Human

Based on animal carcinogenesis bioassays, and using a linear, nonthreshold model, the U.S. EPA (1979) has estimated the following ambient water levels of chloroalkyl ethers which will produce an increased cancer risk of 10^{-5}: BCIE, 11.5µg/l; BCEE, 0.42 µg/l; and BCME 0.02 ng/l.

Eight-hour TWA exposure values (TLV) for the following chloroalkyl ethers have been recommended by the American Conference of Governmental and Industrial Hygienists (ACGIH, 1978): BCME, 1 ppb; BCEE, 5 ppm.

B. Aquatic

Freshwater and saltwater drafted criteria have not been derived for any chloroalkyl ethers because of insufficient data (U.S. EPA, 1979).

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No. 42

Chlorobenzene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
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APRIL 30, 1980

DISCLAIMER

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CHLOROBENZENE

Summary

There is little data on the quantities of chlorobenzene in air, water and food, although this compound has been identified in these media. Chronic exposure to chlorobenzene appears to cause a variety of pathologies under different experimental regimens; however, the liver and kidney appear to be affected in a number of species. There have been no studies conducted to evaluate the mutagenic, teratogenic, or carcinogenic potential of chlorobenzene.

Four species of freshwater fish have 96-hour LC_{50} values ranging from 24,000 to 51,620 µg/l. Hardness does not significantly affect the values. In saltwater, a fish and shrimp had reported 96-hour LC_{50} values of 10,500 µg/l and 6,400 µg/l, respectively. No chronic data involving chlorobenzene are available. Algae, both fresh and saltwater, are considerably less sensitive to chlorobenzene toxicity than fish and invertebrates.

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Chlorinated Benzenes (U.S. EPA, 1979).

Chlorobenzene, most often referred to as monochlorobenzene (MCB; C_6H_5Cl; molecular weight 112.56), is a colorless liquid with a pleasant aroma. Monochlorobenzene has a melting point of -45.6°C, a boiling point of 131-132°C, a water solubility of 488 mg/l at 25°C, and a density of 1.107 g/ml. Monochlorobenzene has been used as a synthetic intermediate in the production of phenol, DDT, and aniline. It is also used as a solvent in the manufacture of adhesives, paints, polishes, waxes, diisocyanates, pharmaceuticals and natural rubber (U.S. EPA, 1979).

Data on current production derived from U.S. International Trade Commission reports show that between 1969 and 1975, the U.S. annual production of monochlorobenzene decreased by 50 percent, from approximately 600 million pounds to approximately 300 million pounds (U.S. EPA, 1977).

II. EXPOSURE

A. Water

Based on the vapor pressure, water solubility, and molecular weight of chlorobenzene, Mackay and Leinonen (1975) estimated the half-life of evaporation from water to be 5.8 hours. Monochlorobenzene has been detected in ground water, "uncontaminated" upland water, and in waters contaminated either by industrial, municipal or agricultural waste. The concentrations ranged from 0.1 to 27 µg/l, with raw waters having the lowest concentration and municipal waste the highest (U.S. EPA, 1975, 1977). These estimates should be considered as gross estimates of exposure, due to the volatile nature of monochlorobenzene.

B. Food

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor of monochlorobenzene to be 13 for the edible portions of fish and shellfish consumed by Americans. This estimate was based on octanol/-water partition coefficients.

C. Inhalation

Data have not been found in the available literature which deal with exposure to chlorobenzene outside of the industrial working environment.

III. PHARMACOKINETICS

A. Absorption

There is little question, based on human effects and mammalian toxicity studies, that chlorobenzene is absorbed through the lungs and from the gastrointestinal tract (U.S. EPA, 1977).

B. Distribution

Because chlorobenzene is highly lipophilic and hydrophobic, it would be expected that it would be distributed throughout total body water space, with body lipid providing a deposition site (U.S. EPA, 1979).

C. Metabolism

Chlorobenzene is metabolised via an NADPH-cytochrome P-448 dependent microsomal enzyme system. The first product, and rate limiting step, is a epoxidation; this is followed by formation of diphenolic and monophenolic compounds (U.S. EPA, 1979). Various conjugates of these phenolic derivatives are the primary excretory products (Lu, et al. 1974). Evidence indicates that the metabolism of monochlorobenzene results in the formation of toxic intermediates (Kohli, et al. 1976). Brodie, et al. (1971) induced microsomal enzymes with phenobarbital and showed a potentiationin in the toxicity of monochlorobenzene. However, the use of 3-methylcho-

lanthrene to induce microsomal enzymes provided protection for rats (Oesch, et al. 1973). The metabolism of chlorobenzene may also lead to the formation of carcinogenic active intermediates (Kohli, et al. 1976).

D. Excretion

The predominant route of elimination is through the formation of conjugates of the metabolites of monochlorobenzene and elimination of these conjugates by the urine (U.S. EPA, 1979). The types of conjugates formed vary with species (Williams, et al. 1975). In the rabbit, 27 percent of an administered dose appeared unchanged in the expired air (Williams, 1959).

IV. EFFECTS

Pertinent data could not be located in the available literature on the carcinogenicity, mutagenicity, teratogenicity, or other reproductive effects of chlorobenzene.

A. Chronic Toxicity

Data on the chronic toxicity of chlorobenzene is sparse and somewhat contradictory. "Histopathological changes" have been noted in lungs, liver and kidneys following inhalation of monochlorobenzene (200, 475, and 1,000 ppm) in rats, rabbits and guinea pigs (Irish, 1963). Oral administration of doses of 12.5, 50 and 250 mg/kg/day to rats produced little pathological change, except for growth retardation in males (Knapp, et al. 1971).

B. Other Relevant Information

Chlorobenzene appears to increase the activity of microsomal NADPH-cytochrome P-450 dependent enzyme systems. Induction of microsomal enzyme activity has been shown to enhance the metabolism of a wide variety of drugs, pesticides and other xenobiotics (U.S. EPA, 1979).

V. AQUATIC TOXICITY

A. Acute Toxicity

Pickering and Henderson (1966) reported observed 96-hour LC_{50} values for goldfish, Carassius auratus, guppy, Poecilia reticulatus, and bluegill, Lepomis macrochirus, to be 51,620, 45,530, and 24,000 µg/l, respectively, for chlorobenzene. Two 96-hour LC_{50} values for chlorobenzene and fathead minnows, Pimephales promelas, are 33,930 µg/l in soft water (20 mg/l) and 29,120 µg/l in hard water (360 mg/l), indicating that hardness does not significantly affect the acute toxicity of chlorobenzene (U.S. EPA, 1978). With Daphnia magna, an observed 48-hour EC_{50} value of 86,000 µg/l was reported. In saltwater studies, sheepshead minnow had a reported unadjusted LC_{50} (96-hour) value of 10,500 µg/l, with a 96-hour EC_{50} of 16,400 µg/l for mysid shrimp (U.S. EPA, 1978).

B. Chronic Toxicity

No chronic toxicity studies have been reported on the chronic toxicity of chlorobenzene and any salt or freshwater species.

C. Plant Effects

The freshwater alga Selenastrum capricornutum is considerably less sensitive than fish and Daphnia magna. Based on cell numbers, the species has a reported 96-hour EC_{50} value of 224,000 µg/l. The saltwater alga, Skeletonema costatum, had a 96-hour EC_{50}, based on cell numbers of 341,000 µg/l.

D. Residues

A bioconcentration factor of 44 was obtained assuming an 8 percent lipid content of fish.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

The American Conference of Governmental Industrial Hygienists (ACGIH, 1971) threshold limit value for chlorobenzene is 350 mg/m^3. The acceptable daily intake (ADI) was calculated to be 1.008 mg/day. The U.S. EPA (1979) draft water criterion for chlorobenzene is 20 µg/l, based on threshold concentration for odor and taste.

B. Aquatic

For chlorobenzene, the drafted criterion to protect freshwater aquatic life is 1,500 µg/l as a 24-hour average; the concentration should not exceed 3,500 µg/l at any time. To protect saltwater aquatic life, a draft criterion of 120 µg/l as a 24-hour average with a concentration not exceeding 280 µg/l at any time has been recommended (U.S. EPA, 1979).

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No. 43

p-Chloro-m-cresol

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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SUMMARY

p-Chloro-m-cresol has been found to be susceptible to biodegradation under aerobic conditions in a synthetic sewage sludge. It has been found to be formed by the chlorination of waters receiving effluents from electric power-generating plants and by the chlorination of the effluent from a domestic sewage treatment facility.

Very little information on the health effects of p-chloro-m-cresol was located. p-Chloro-m-cresol has been characterized as very toxic in humans, although support for this statement is limited. In rats, a subcutaneous LD_{50} of 400 mg/kg and an oral LD_{Lo} of 500 mg/kg have been reported.

I. INTRODUCTION

p-Chloro-m-cresol (4-chloro-3-methylphenol; C_7H_7ClO; molecular weight 142.58) is a solid (dimorphous crystals) at room temperature. The pure compound is odorless, but it has a phenolic odor in its most common, impure form. Its melting point is 55.5°C and its boiling point is 235°C. It is soluble in water and many organic solvents (Windholz 1976).

A review of the production range (includes importation) statistics for p-chloro-m-cresol (CAS No. 59-50-7) as listed in the initial TSCA Inventory (U.S. EPA 1979) shows that between 10,000 and 90,000 pounds of this chemical were produced/imported in 1977.*

p-Chloro-m-cresol is used as an external germicide and as a preservative for glues, gums, paints, inks, textiles and leather goods (Hawley 1971). It is also used as a preservative in cosmetics (Wilson 1975, Liem 1977). EPA (1973) indicates that p-chloro-m-cresol is "cleared for use in adhesives used in food packaging."

*This production range information does not include any production/importation data claimed as confidential by the person(s) reporting for the TSCA Inventory, nor does it include any information which would compromise Confidential Business Information. The data submitted for the TSCA Inventory, including production range information, are subject to the limitations contained in the Inventory Reporting Regulations (40 CFR 710).

II. EXPOSURE

A. Environmental Fate

Voets et al. (1976) reported that p-chloro-m-cresol was quite susceptible to microbial breakdown under aerobic conditions in an organic medium (synthetic sewage sludge), while degradation under aerobic conditions in a mineral solution (simulating oligotrophic aquatic systems) was relatively difficult. No degradation was observed in either system under anaerobic conditions.

B. Bioconcentration

No studies on the bioconcentration potential of this compound were found. Based on its solubility, p-chloro-m-cresol would not be expected to have a high bioconcentration potential.

C. Exposure

Human exposure to p-chloro-m-cresol occurs through its presence in certain cosmetics and in a variety of other consumer products in which it is used as a preservative (Wilson 1975, Liem 1977).

p-Chloro-m-cresol has been found to be formed by the chlorination of water from a lake and a river receiving cooling waters from electric power-generating plants, at concentrations of 0.2 ug/l and 0.7 ug/l, respectively. It has also been found to be formed by the chlorination of the effluent from a domestic sewage treatment facility at a concentration of 1.5 ug/l (Jolley et al. 1975).

III. PHARMACOKINETICS

No information was found.

IV. HEALTH EFFECTS

Very little toxicological data for p-chloro-m-cresol was available. The subcutaneous LD_{50} for p-chloro-m-cresol in rats is 400 mg/kg (NIOSH 1975). The oral LD_{Lo} for p-chloro-m-cresol in rats is 500 mg/kg. In mice the intraperitoneal LD_{Lo} is 30 mg/kg and the subcutaneous LD_{Lo} is 200 mg/kg

(U.S. DHEW 1978). One author has rated p-chloro-m-cresol as very toxic, with a probable lethal dose to humans of 50-500 mg/kg. (Von Oettingen as quoted in Gosselin et al. 1976). p-Chloro-m-cresol was also reported as non-irritating to skin in concentrations of 0.5 to 1.0% in alcohol.

V. AQUATIC TOXICITY

A. Acute

The only information available is that for Daphnia pulex. The 96-hour LC_{50} for p-chloro-m-cresol exposure is 3.1 mg/L (Jolley et al. 1977).

VI. GUIDELINES

No guidelines for exposure to p-chloro-m-cresol were located.

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No. 44

Chloroethane

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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CHLOROETHANE

SUMMARY

There is no available evidence which indicates that monochloroethane produces carcinogenic, mutagenic, or teratogenic effects. Symptoms produced by human poisoning with monochloroethane include central nervous system depression, respiratory failure, and cardiac arrhythmias. The results of animal studies indicate that liver, kidney, and cardiac toxicity may be produced by monochloroethane.

Data examining the toxic effects of chloroethane on aquatic organisms were not available.

CHLOROETHANE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Chlorinated Ethanes (U.S. EPA, 1979a).

The chloroethanes are hydrocarbons in which one or more of the hydrogen atoms have been replaced by chlorine atoms. Water solubility and vapor pressure decrease with increasing chlorination, while density and melting point increase. Monochloroethane (chloroethane, M.W. 64.52) is a gas at room temperature. The compound has a boiling point of 13.1°C, a melting point of -138.7°C, a specific gravity of 0.9214, and a solubility of 5.74 g/l in water (U.S. EPA, 1979a).

The chloroethanes are used as solvents, cleaning and degreasing agents, and in the chemical synthesis of a number of compounds.

The 1976 production of monochloroethane was 335×10^3 tons/year (U.S. EPA, 1979a).

The chlorinated ethanes form azeotropes with water (Kirk and Othmer, 1963). All are very soluble in organic solvents (Lange, 1956). Microbial degradation of the chlorinated ethanes has not been demonstrated (U.S. EPA, 1979a).

The reader is referred to the Chlorinated Ethanes Hazard Profile for a more general discussion of chlorinated ethanes (U.S. EPA, 1979b).

II. EXPOSURE

The chloroethanes present in raw and finished waters are due primarily to industrial discharges. Small amounts of the chloroethanes may be formed by chlorination of drinking water

or treatment of sewage. Air levels of chloroethanes are produced by evaporation of these volatile compounds widely used as degreasing agents and in dry cleaning operations (U.S. EPA, 1979a).

Sources of human exposure to chloroethanes include water, air, contaminated foods and fish, and dermal absorption. Fish and shellfish have shown levels of chloroethanes in the nanogram range (Dickson and Riley, 1976). Data on the levels of monochloroethanes in foods is not available.

An average bioconcentration factor for monochloroethane in fish and shellfish has not been derived by the EPA.

III. PHARMACOKINETICS

Pertinent data could not be located in the available literature on monochloroethane for absorption, distribution, metabolism, and excretion. However, the reader is referred to a more general treatment of chloroethanes (U.S. EPA, 1979b), which indicates rapid absorption of chloroethanes following oral or inhalation exposure; widespread distribution of the chloroethanes throughout the body; enzymatic dechlorination and oxidation to the alcohol and ester forms; and excretion of the chloromethanes primarily in the urine and expired air. Specifically for monochloroethane, absorption following dermal application is minor; and excretion appears to be rapid, with the major portion of the injected compound excreted in the first 24 hours (U.S. EPA, 1979a).

IV. EFFECTS

Pertinent data could not be located in the available literature on monochloroethane for carcinogenicity, mutagenicity, teratogenicity and other reproductive effects.

A. Chronic Toxicity

Human symptons of monochloroethane poisoning indicate central nervous system depression, respiratory failure, and cardivascular symptoms, including cardiac arrhythmias (U.S. EPA, 1979a). Animal toxicity has indicated kidney damage and fatty infiltration of the liver, kidney, and heart (U.S. EPA, 1979a).

V. AQUATIC TOXICITY

Pertinent data could not be located in the available literature.

VI. EXISTING GUIDLINES AND STANDARDS

A. Human

The eight-hour TWA standard prepared by OSHA for monochloroethane is 1,000 ppm.

Sufficient data are not available to derive a criterion to protect human health from exposure to monochloroethane in ambient water.

B. Aquatic

There are not sufficient toxicological data to calculate exposure criteria.

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No. 45

Chloroethene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
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APRIL 30, 1980

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CHLOROETHENE

(VINYL CHLORIDE)

Summary

Vinyl chloride has been used for over 40 years in the production of polyvinyl chloride. Animal studies indicate that vinyl chloride is not teratogenic, but it has been found to be mutagenic in several biologic test systems. Vinyl chloride has been found to be carcinogenic in laboratory animals and has been positively associated with angiosarcoma of the liver in humans. Recently "vinyl chloride disease", a multisystem disorder, has been described in workers exposed to vinyl chloride.

Data are lacking concerning the effects of vinyl chloride in freshwater and saltwater aquatic life.

CHLOROETHENE

(VINYL CHLORIDE)

I. INTRODUCTION

Vinyl chloride (CH_2CHCl; molecular weight 62.5) is a highly flammable chloro-olefinic hydrocarbon which emits a sweet or pleasant odor, and has a vapor density slightly more than twice that of air. Its physical properties include: melting point, -153.8°C; and solubility in water, 0.11g/100 g at 28°C. It is soluble in alcohol and very soluble in ether and carbon tetrachloride (Weast, 1972). Many salts of metals (including silver, copper, iron, platinum, iridium) have the ability to complex with vinyl chloride resulting in its increased solubility in water. Conversely, alkali metal salts, such as sodium or potassium chloride, may decrease the solubility of vinyl chloride in aqueous solutions (Fox, 1978).

Vinyl chloride has been used for over 40 years in the production of polyvinyl chloride (PVC), which in turn is the most widely used material in the manufacture of plastics. Production of vinyl chloride in the U.S. reached slightly over 5 billion pounds in 1977 (U.S. Int. Trade Comm, 1978).

Vinyl chloride and polyvinyl chloride are used in the manufacture of numerous products in building and construction, the automotive industry, for electrical wire insulation and cables, piping, industrial and household equipment, packaging for food products, medical supplies, and are depended upon heavily by the rubber, paper and glass industries (Maltoni, 1976a).

In the U.S. about 1500 workers were employed in monomer synthesis and an additional 5000 in polymerization operations (Falk,

et al. 1974). As many as 350,000 workers were estimated to be associated with fabricating plants (U.S. EPA, 1974). By 1976, it was estimated that worldwide nearly one million persons were associated with manufacturing goods derived from PVC (Maltoni, 1976a). Potential sources of population exposure to vinyl chloride are emissions from PVC fabricating plants, release of monomers from various plastic products, and emissions from the incineration of PVC products (U.S. EPA, 1975).

II. EXPOSURE

A. Water

Small amounts of vinyl chloride may be present in public water supplies as a result of industrial waste water discharges. The levels of vinyl chloride in effluents vary considerably depending on the extent of in-plant treatment of waste water. Vinyl chloride in samples of waste water from seven areas ranged from 0.05 ppm to 20 ppm, typical levels being 2-3 ppm (U.S. EPA, 1974). The low solubility and high volatility of vinyl chloride tend to limit the amounts found in water; however, the presence of certain salts may increase the solubility and therefore could create situations of concern (U.S. EPA, 1975).

Polyvinyl chloride pipe used in water distribution systems provides another source of low levels of vinyl chloride in drinking water. In a study by the U.S. EPA of five water distribution systems which used PVC pipes, water from the newest, longest pipe system had the highest vinyl chloride concentration (1.4 µg/l) while the two oldest systems only had traces of vinyl chloride (0.3 µg/l and 0.6 µg/l) (Dressman and McFarren, 1978). The National

Science Foundation (NSF) has adopted a voluntary standard of 10 ppm or less of residual monomer in finished pipe and fittings. Three times a year NSF samples water supplies in several cities. In 1977, more than 95 percent of the samples conformed to the standard; however, levels of 5.6 μg/l and 0.27 μg/l vinyl chloride have been detected in at least two cities.

B. Food

Small quantities of vinyl chloride are ingested by humans when the entrained monomer migrates into foods packaged in PVC wrappings and containers. The solubility of vinyl chloride in foods packaged in water is low (0.11 percent); however, the monomer is soluble in alcohols and mineral oil. In 1973, the U.S. Treasury Department banned the use of vinyl chloride polymers for packaging alcoholic beverages (Int. Agency Res. Cancer, 1974). The FDA analyzed a number of PVC packaged products in 1974. The concentrations ranged from "not detectable" to 9,000 ppb.

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor of vinyl chloride to be 1.9 for the edible portions of fresh and shellfish consumed by Americans. This estimate was based on the octanol/water coefficient of vinyl chloride.

C. Inhalation

Inhalation of vinyl chloride is the principal route of exposure to people working in or living near vinyl chloride industries. After 1960, Dow Chemical Co. was successful in reducing exposures to workers to about 25 ppm level, though levels up to 500 ppm still occurred. Inhalation exposures drastically dropped after appropriate controls were instituted following case reports of vinyl chloride induced angiosarcoma of the liver in workers and experimental animals (U.S. EPA, 1979).

III. PHARMACOKINETICS

A. Absorption

Vinyl chloride is rapidly absorbed through the lungs and enters the blood stream (Duprat, et al. 1977).

B. Distribution

The liver of rats accumulates the greatest percentage of vinyl chloride and/or metabolites of vinyl chloride 72 hours after a single oral dose (Watanabe, et al. 1976). Ten minutes after a 5-minute inhalation exposure to vinyl chloride at 10,000 ppm, the compound was found in the liver, bile duct, stomach, and kidney of rats (Duprat, et al. 1977). Immediately after exposure by inhalation to ^{14}C-vinyl chloride at 50 ppm for 5 hours, the percent incorporated as ^{14}C/radioactivity per gram of tissue was highest for kidney (2.13), liver (1.86), and spleen (0.73). Forty-eight hours after the beginning of exposure, labeled material could still be detected in these tissues.

C. Metabolism

Detoxification of vinyl chloride takes place primarily in the liver by oxidation to polar compounds which can be conjugated to glutathione and/or cysteine (Hefner, et al. 1975). These covalently bond metabolites are then excreted in the urine.

Vinyl chloride is metabolized extensively by rats in vivo and the metabolic pathways appear to be saturable. The postulated primary metabolic pathway involves alcohol dehydrogenase and, for rats, appears to be saturated by exposures to concentrations exceeding 220 to 250 ppm. In rats exposed to higher concentrations, metabolism of vinyl chloride is postulated to occur via a secondary

pathway involving epoxidation and/or peroxidation. Present data indicates that vinyl chloride is metabolized to an activated carcinogen electrophile and is capable of covalent reaction with nucleophilic groups or cellular macromolecules (U.S. EPA, 1979).

There is ample evidence that the mixed function oxidase (MFO) system may be involved in the metabolism of vinyl chloride. Rat liver microsomes catalyze the covalent binding of vinyl chloride metabolites to protein and nucleic acids; chloroethylene oxide is thought to be the primary microsomal metabolite capable of alkylating these cellular macromolecules (Kappus, et al. 1975; 1976; Laib and Bolt, 1977). Hathway (1977) reports in vitro depurination of calf thymus DNA by chloroacetaldehyde identical to that observed in hepatocyte DNA following the administration of vinyl chloride to rats in vitro.

D. Excretion

Watanabe, et al. (1976) monitored the elimination of vinyl chloride for 72 hours following a single oral dose administered to rats. The total ^{14}C-activity recovered at each dose level ranged from 82-92 percent. At a dose level of 1 mg/kg, 2 percent was exhaled as vinyl chloride, 13 percent was exhaled as carbon dioxide, 59 percent was eliminated in the urine and 2 percent in the feces. Excretion of vinyl chloride at a dose level of 100 mg/kg was 66 percent exhaled as vinyl chloride, 2.5 percent as carbon dioxide, 11 percent in the urine and 0.5 percent in the feces. Administration by inhalation produced almost the same results.

Green and Hathway (1975) found that more than 96 percent of 250 µg ^{14}C-vinyl chloride administered via intragastric, intra-

venous or intraperitoneal routes was excreted within 24 hours. The rats given vinyl chloride by the intragastric route exhaled 3.7 percent as vinyl chloride, 12.6 percent as CO_2; 71.5 percent of the labeled material was in the urine and 2.8 percent in the feces. Intravenous injections resulted in 9.9 percent exhaled as vinyl chloride, 10.3 percent as CO_2; 41.5 percent in the urine and 1.6 percent in the feces.

IV. EFFECTS

A. Carcinogenicity

The carcinogenicity of vinyl chloride has been investigated in several animal studies. Viola, et al. (1971) induced skin epidermoid carcinomas, lung carcinomas or bone steochrondromas in 24/25 male rats exposed to 30,000 ppm vinyl chloride intermittently for 12 months. Tumors appeared between 10 and 11 months. Caputo, et al. (1974) observed carcinomas and sarcomas in all groups of male and female rats inhaling various concentrations of vinyl chloride except those exposed to 50 ppm.

Maltoni and Lefemine (1974a,b; 1975) reported on a series of experiments concerning the effects on rats, mice, and hamsters of inhalation exposure to vinyl chloride at concentrations ranging from 50 to 10,000 ppm for varying periods of time. The animals were observed for their entire lifetime. Angiosarcomas of the liver occurred in all three species, as well as tumors at several other sites. A differential response between the sexes was not reported.

Maltoni (1976b) observed four subcutaneous angiosarcomas, four zymbal gland carcinomas, and one nephroblastoma in

66 offspring of rats exposed by inhalation 4 hours/day to 10,000 or 6,000 ppm vinyl chloride from the 12th to 18th day of gestation. Liver angiosarcomas were also observed in rats administered vinyl chloride via stomach tube for 52 weeks.

Recent experiments by Lee, et al. (1977) with rats and mice confirm the carcinogenicity of vinyl chloride. Each species was exposed to 50,250 or 1000 ppm vinyl chloride or 55 ppm vinylene chloride 6 hr/day, 5 days/week for 1-12 months. After 12 months, bronchioalveolar adenomas, mammary gland tumors, and angiosarcomas in the liver and other sites developed in mice exposed to all three dose levels of vinyl chloride. Rats exposed to 250 ppm or 100 ppm vinyl chloride developed angiosarcoma in the liver, lung and other sites (Lee, et al. 1978).

The primary effect associated with vinyl chloride exposure in man is an increased risk of cancer in several organs including angiosarcoma of the liver. Liver angiosarcoma is an extremely rare liver cancer in humans, with 26 cases reported annually in the U.S. (Natl. Cancer Inst., 1975). Human data on the carcinogenic effects of vinyl chloride have been obtained primarily from cases of occupational exposures of workers. The latent period has been estimated to be 15-20 years; however, recent case reports indicate a longer average latent period (Spirtas and Kaminski, 1978).

A number of epidemiological studies of vinyl chloride have been reported (U.S. EPA, 1979). Tabershaw/Cooper Associates (1974) found no increase in the overall mortality rate for vinyl chloride workers nor significant increases in standard mortality

rates (SMR's) for malignant neoplasms. Reexamination of this data by Ott, et al. (1975) including more clearly defined exposure levels confirmed the previous findings: no increase over that expected for malignant neoplasms in the low exposure group (TWA 10-100 ppm vinyl chloride) and a non-significant increase in deaths due to malignant neoplasms in the high exposure group (TWA, greater than 200 ppm).

However, liver cancer death were twelve-fold, and brain cancer deaths were five-fold greater than that expected in a study by Wagoner (1974). Likewise, Monson, et al. (1974) found death due to cancer to be 50 percent higher than expected in vinyl chloride workers who died from 1947-1973, including a 900 percent increase in cancers of the liver and biliary tract.

In the most recent update of the NIOSH register, a total of 64 cases of hepatic angiosarcoma have been identified worldwide among vinyl chloride exposed industrial workers (Spirtas and Kaminski, 1978). Twenty-three of these cases were reported in the United States. Six cases were documented since 1975.

B. Mutagenicity

Vinyl chloride has been found to be mutagenic in a number of biological systems including: metabolically activated systems using Salmonella typhimurium; back mutation systems using Escherichia coli; forward mutation and gene coversion in yeast; and germ cells of Drosophila and Chinese hamster V79 cells (U.S. EPA, 1979).

The dominant lethal assay was used to test the mutagenicity of inhaled vinyl chloride in mice. Levels as high as 30,000

ppm (6 hours/day for 5 days) yielded negative results (Anderson, et al. 1976).

Several investigators have observed a significantly higher incidence of chromosomal aberrations in the lymphocytes of workers chronically exposed to high levels of vinyl chloride (Ducatman, et al. 1975; Purchase, et al. 1975; Funes-Cravioto, et al. 1975).

C. Teratogenicity

Animal studies using mice, rats and rabbits, indicate that inhalation of vinyl chloride does not induce gross teratogenic abnormalities in offspring of mothers exposed 7 hours daily to concentrations ranging from 50 to 2,500 ppm (John, et al. 1977); however, excess occurrences of minor skeletal abnormalities were noted. Increased fetal death was noted at the higher exposure levels. These findings were confirmed by Radike, et al. (1977a) who exposed rats to 600-6,000 ppm vinyl chloride, 4 hours daily on the 9th to the 21st day of gestation.

Further examination is needed of reported high rates of congenital defects in three small communities in which vinyl chloride polymerization plants are located (U.S. EPA, 1979).

D. Other Reproductive Effects

No effect on fertility in mice was noted in a dominant lethal assay conducted by Anderson, et al. (1976).

E. Chronic Toxicity

There are numerous clinical indications that chronic exposure to vinyl chloride is toxic to humans (U.S. EPA, 1979). Hepatitis-like changes, angioneurosis, Raynaud's syndrome, derma-

titis, acroosteolysis, thyroid insufficiency, and hepatomegaly have been reported around the world. Other long term effects include functional disturbances of the central nervous system with adrenergic sensory polyneuritis (Smirnova and Granik, 1970); thrombocytopenia, splenomegaly, liver malfunction with fibrosis, pulmonary changes (Lange, et al. 1974); and alterations in serum enzyme levels (Makk, et al. 1976).

F. Other Relevant Information

Pretreatment of rats with pyrazole (an alcohol dehydrogenose inhibitor) and ethanol inhibits the metabolism of vinyl chloride (Hefner, et al. 1975). This indicates the involvement of alcohol dehydrogenose in the metabolism of vinyl chloride.

The chronic ingestion of alcohol was found to increase the incidence of liver tumors and tumors in other sites in individuals exposed to vinyl chloride (Radike, 1977b).

Jaeger (1975) conducted experiments to determine the interaction between vinylidene chloride (1,1-DCE) and vinyl chloride. In this experiment, the effects of 4-hour exposures to 200 ppm of 1,1-DCE and 1,000 ppm vinyl chloride were less than if 1,1-DCE was given alone.

V. AQUATIC TOXICITY

A. Pertinent information relevant to acute and chronic toxicity, plant effects and residues for vinyl chloride were not found in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The current federal OSHA standard for vinyl chloride is 1 ppm (TWA) with a maximum of 5 ppm for a period of no longer than 15 minutes in 1 day. (39 FR 35890 (Oct. 4, 1979)).

In 1974, a notice to cancel registrations of pesticide spray products containing vinyl chloride as a propellant was issued (39 FR 14753 (April 26, 1974)). Other aerosol products, such as hair spray, utilizing vinyl chloride as a propellant were banned from the market in the U.S. and other countries (Int. Agency Res. Cancer, 1974). The U.S. EPA proposed in 1975 and 1976 an emission standard of 10 ppm vinyl chloride at the stack for industry.

The draft ambient water quality criterion for vinyl chloride has been set to reduce the human lifetime cancer risk level to 10^{-5}, 10^{-6} and 10^{-7} (U.S. EPA, 1979). The corresponding criteria are 517 µg/l, 51.7 µg/l and 5.17 µg/l, respectively. The data base from which this criterion has been derived is currently being reviewed, therefore, this criteria to protect human health may change.

B. Aquatic

Fresh or salt water criteria could not be derived because of insufficient data (U.S. EPA, 1979).

CHLOROETHENE
(VINYL CHLORIDE)

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No. 46

2-Chloroethyl Vinyl Ether

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

2-CHLOROETHYL VINYL ETHER

SUMMARY

Very little information is available for 2-chloroethyl vinyl ether. It appears to be relatively stable except under acidic conditions. There is some potential for bioconcentration of the compound in exposed organisms. No exposure data were available, although 2-chloroethyl vinyl ether has been identified in industrial effluent discharges.

The acute toxicity of 2-chloroethyl vinyl ether is relatively low: oral LD_{50}: 250 mg/kg; dermal LD_{50} 3.2 mL/kg; LC_{LO}: 250 ppm (4 hrs). Eye irritation has been reported following exposure to 2-chloroethyl vinyl ether. No other data on health effects were available.

I. INTRODUCTION

2-Chloroethyl vinyl ether ($ClCH_2CH_2OCH=CH_2$; molecular weight 106.55) is a liquid having the following physical/chemical properties (Windholz, 1976; Weast, 1972; U.S. EPA, 1979c):

Boiling point (760 mm Hg):	109°C
Melting point:	-70°C
Density:	1.0475^{20}
Solubility:	Soluble in water to the extent of 6g/L; very soluble in alcohol and ether

The compound finds use in the manufacture of anesthetics, sedatives, and cellulose ethers (Windholz, 1976).

A review of the production range (includes importation) statistics for 2-chloroethyl vinyl ether (CAS No. 110-75-8) which is listed in the initial TSCA inventory (1979a) has shown that none of this chemical was produced or imported in 1977*.

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*This production range information does not include any production/importation data claimed as confidential by the person(s) reporting for the TSCA Inventory, nor does it include any information which would compromise confidential business information. The data submitted for the TSCA Inventory, including production range information, are subject to the limitations contained in the Inventory Reporting Regulations (40CFR710).

II. EXPOSURE

A. Environmental Rate

The β-chloroalkyl ethers have been shown to be quite stable to hydrolysis and to persist for extended periods without biodegradation (U.S. EPA, 1979b). 2-Chloroethyl ethyl ether (a β-chloroalkyl other) is stable to sodium hydroxide solutions but will undergo hydrolysis in the presence of dilute acids to acetaldehyde and 2-chloroethanol (Windholz 1976). Conventional treatment systems may be inadequate to sufficiently remove the β-chloroalkyl ethers once present in water supplies (U.S. EPA 1979b; U.S. EPA 1975).

B. Bioconcentration

A calculated bioconcentration factor of 34.2 (U.S. EPA, 1979b) points to some potential for 2-chloroethyl vinyl ether accumulation in exposed organisms.

C. Environmental Occurrence

There is no specific information available on general population exposure to 2-chloroethyl vinyl ether. The compound has been identified three times in the water of Louisville, Kentucky (3/74): twice in effluent facturing plants and once in the effluent from a latex plant (U.S. EPA 1976). No concentration levels were given.

NIOSH, utilizing data from the National Occupational Hazards Survey (NOHS 1977) has compiled a listing summarizing occupational exposure to 2-chloroethyl vinyl ether (Table 1). As shown, NIOSH estimates 23,473 people are exposed annually to the compound. The number of potentially exposed individuals is greatest for the following areas: fabricated metal products; wholesale trade; leather, rubber and plastic, and chemical products.

III. PHARMACOKINETICS

Vinyl ethers readily undergo acid catalysed hydrolysis to give alcohols and aldehydes, e.g., 2-chloroethyl vinyl ether is hydrolyzed to 2-chloroethanol and acetaldehyde (Salomaa et al. 1966).

TABLE 1

PROJECTED NUMBERS BY INDUSTRY

HAZARD DESCRIPTION

84673 Chloroethyl Vinyl Ether, 2-

SIC CODE	DESCRIPTION	ESTIMATED PLANTS	ESTIMATED PEOPLE	ESTIMATED EXPOSURES
25	Furniture and fixtures	193	920	920
28	Chemicals and allied products	103	1,683	1,683
30	Rubber and plastic products	89	1,669	1,669
31	Leather and leather products	45	2,279	2,279
34	Fabricated metal products	61	9,149	9,149
35	Machinery, except electrical	35	35	35
36	Electrical equipment and supplies	54	432	432
37	Transportation equipment	92	553	553
38	Instruments and related products	24	299	299
39	Miscellaneous manufacturing industries	119	240	240
50	Wholesale trade	1,239	6,194	6,194
73	Miscellaneous business services	5	20	20
TOTAL		2,059	23,473	23,473

IV. HEALTH EFFECTS

A. Mutagenicity

Although no information on the mutagenicity of 2-chloroethyl vinyl ether was available, its hydrolysis product, 2-chloroethanol, has been shown to be mutagenic in Salmonella typhimurium TA 1535 (Rannug et al. 1976), TA100 and TA98 (McCann et al. 1976), as well as Klebsiella pneumonia (Voogd et al. 1972).

B. Other Toxicity

Very little toxicological data for 2-chloroethyl vinyl ether is available. The oral LD_{50} for 2-chloroethyl vinyl ether in rats is 250 mg/kg (U.S. EPA, 1975, Patty 1963). Dermal exposure to the shaven skin of rabbits for 24 hours resulted in an LD_{50} of 3.2 mL/kg (U.S. EPA, 1976). The acute inhalation toxicity of 2-chloroethyl vinyl ether in rats was determined following single four-hour exposures. The lowest lethal concentration was 250 ppm (U.S. EPA, 1975). In a similar inhalation study, 1/6 rats exposed by inhalation to 500 ppm died during the 14-day observation period (U.S. EPA, 1975).

Primary skin irritation and eye irritation studies have also been conducted for 2-chloroethyl vinyl ether. Dermal exposure to undiluted 2-chloroethyl vinyl ether did not cause even slight erythema. Application of 0.5 mL undiluted 2-chloroethyl vinyl ether to the eyes of rabbits resulted in severe eye injury (U.S. EPA, 1975).

V. AQUATIC TOXICITY

A. Acute

The adjusted 96-hour LC_{50} for blue gill exposure to 2-chloroethyl vinyl ether is 194,000 ug/L (U.S. EPA, 1979b). Dividing by the species sensitivity factor (3.9), a Final Fish Acute Value of 50,000 ug/L is obtained (Table 1). There is no data on invertebrate or plant exposure.

VI. EXISTING GUIDELINES

No guidelines were located.

Table 2. Freshwater fish acute values (U.S. EPA, 1979b)

Organism	Bioassay Method	Test Conc.**	Chemical Description	Time (hrs)	LC_{50} (ug/L)	Adjusted LC_{50} (ug/L)
Bluegill, *Lepomis macrochirus*	S	U	2-chloroethyl vinyl ether	96	354,000	194,000

* S = static

** U = unmeasured

Geometric mean of adjusted values: 2-chloroethyl vinyl ether = 194,000 ug/L

$\frac{194,000}{3.9}$ = 50,000 ug/L

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No. 47

Chloroform (Carbon Trichloromethane)

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated chloroform and has found sufficient evidence to indicate that this compound is carcinogenic.

CHLOROFORM

SUMMARY

Chloroform has been found to induce hepatocellular carcinomas in mice and kidney epithelial tumors in rats. Hepatomas have also been induced in mice, but necrosis may be a prerequisite to tumor formation. Bacterial assays involving chloroform have yielded no mutagenic effects. Chloroform has produced teratogenic effects when administered to pregnant rats.

Reported 96-hour LC_{50} values for two common freshwater fish range from 43,800 to 115,000 µg/l in static tests. A 48-hour static test with Daphnia magna yielded an LC_{50} of 28,900 µg/l. The observed 96-hour LC_{50} for the saltwater pink shrimp is 81,500 µg/l. In a life cycle chronic test, the chronic value was 2,546 µg/l for Daphnia magna. Pertinent information on chloroform toxicity to plants could not be located in the available literature. In the only residue study reported, the bluegill concentrated chloroform six times after a 14-day exposure. The tissue half-life was less than one day suggesting that residues of chloroform would not be an environmental hazard to aquatic life.

CHLOROFORM

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Chloroform (U.S. EPA, 1979a).

Chloroform ($CHCl_3$; molecular weight 119.39) is a clear, colorless liquid with a pleasant, etheric, non-irritating odor and taste (Hardie, 1964; Windholz, 1976). It has the following physical/chemical properties (Hardie, 1964; Irish, 1972; Windholz, 1976):

Boiling Point:	61-62°C
Melting Point:	-63.5°C
Flash Point:	none (none-flammable)
Solubility:	Water - 7.42×10^6 µg/l at 25°C Miscible with alcohol, benzene, ether, petroleum ether, carbon tetrachloride, carbon disulfide, and oils.
Vapor Pressure:	200 mm Hg at 25°C

Current Production: 1.2×10^5 metric tons/year (U.S. EPA, 1978a).

Chloroform is currently used either as a solvent or as an intermediate in the production of refrigerants (principleus), plastics, and pharmaceuticals (U.S. EPA, 1975).

Chloroform is relatively stable under normal environmental conditions. When exposed to sunlight, it decomposes slowly in air but is relatively stable in water. The measured half-life for hydrolyis was found to be 15 months (Natl. Acad. Sci., 1978a). Degradation in water can occur in the presence of metals and is accelerated by aeration (Hardie, 1964).

For additional information regarding halomethanes as a class the reader is referred to the Hazard Profile on halomethanes (U.S. EPA, 1979b).

II. EXPOSURE

Chloroform appears to be ubiquitous in the environment. A major source of chloroform contamination is from the chlorination of water and wastewater (U.S. EPA, 1975; Bellar, et al., 1974). Industrial spills may occasionally be a pulse source of transient high level contamination (Nat. Acad. Sci., 1978a; Neely, et al., 1976; Brass and Thomas, 1978).

Based on available monitoring data including information from the National Organics Monitoring Survey (NOMS), the U.S. EPA (1978b) has estimated the uptake of chloroform by adult humans from air, water, and food:

Source	Adult mg/yr	Percent uptake
	Maximum Conditions	
Atmosphere	204	36
Water	343	61
Food Supply	16	3
Total	563	100.00
	Minimum Conditions	
Atmosphere	0.41	13
Water	0.73	23
Food Supply	2.00	64
Total	3.14	100.00
	Mean Conditions	
Atmosphere	20.0	22
Water	64.0	69
Food Supply	9.00	10
Total	93	100.00

A similar estimate, not using NOMS data, has been made by the National Academy of Sciences (Nat. Acad. Sci., 1978a).

The U.S. EPA (1979a) has estimated the bioconcentration factor for chloroform to be 14 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on measured steady-state bioconcentration studies in bluegills.

III. PHARMACOKINETICS

A. Absorption

The efficiency of chloroform absorption by the gastrointestinal tract is virtually 100 percent in humans (Fry, et al., 1972). The corresponding value by inhalation is 49 to 77 percent (Lehmann and Hassegawa, 1910). Quantitative estimates of dermal absorption efficiency were not encountered. Since chloroform was used as an anesthetic via dermal administration, some dermal absorption by humans can be assumed (U.S. EPA, 1979a).

B. Distribution

Chloroform is transported to all mammalian body organs and is also transported across the placenta. Strain differences for chloroform distribution in mice have been documented by Vessell, et al., (1976).

C. Metabolism

Most absorbed chloroform is not metabolized by mammals. Toxication, rather than detoxication, appears to be the major consequence of metabolism and probably involves mixed-function oxidase (MFO) enzyme systems. This observa-

tion is based on enhancement of chloroform toxicity by MFO inducers and the diminution of toxicity by MFO inhibitors (Ilett, et al., 1973, McLean, 1970). At least in the liver, covalent binding of a metabolite to tissue is associated with tissue damage (Lavigne and Marchand, 1974). Limited human data (two people) suggest that about 50 percent of absorbed chloroform is metabolized to CO_2 (Fry, et al., 1972; Chiou, 1975).

D. Excretion

In humans, the half-life of chloroform in the blood and expired air is 1.5 hours (Chiou, 1975). Most unchanged chloroform and CO_2 generated from chloroform are eliminated via the lungs. Chlorine generated from chloroform metabolism is eliminated via the urine (Taylor, et al., 1974; Fry, et al., 1972).

IV. EFFECTS

A. Carcinogenicity

Eschenbrenner and Miller (1945) demonstrated that oral doses of chloroform administered over a 16-month period induced hepatomas in strain A mice. Based on variations in dosing schedules, these researchers concluded that necrosis was prerequisite to tumor induction.

In the National Cancer Institute bioassay of chloroform (NCI, 1976), hepatocellular carcinomas were induced in mice (Table 1) and kidney epithelial tumors were induced in male rats (Table 2), following oral doses over extended periods of time.

Ten epidemiologic studies have been conducted on the association of human exposure to chloroform and/or other trihalomethanes with cancer. A review of these studies by the National Academy of Sciences (NAS, 1978b) indicated that these studies suggest that higher concentrations of trihalomethanes in drinking water may be associated with an increased frequency of cancer of the bladder. One of these studies (McCabe, 1975) claimed to demonstrate a statistically significant correlation between age, sex, race, adjusted death rate for total cancer, and chloroform levels.

B. Mutagenicity

Chloroform yielded negative results in the Ames assay (Simmon, et al. 1977).

C. Teratogenicity

At oral dose levels causing signs of maternal toxicity, chloroform had fetotoxic effects on rabbits (100 mg/kg/day) and rats (316 mg/kg/day) (Thompson, et al., 1974). Fetal abnormalities (acaudia, imperforate anus, subcutaneous edema, missing ribs, and delayed ossification) were induced when pregnant rats were exposed to airborne chloroform at 489 and 1,466 mg/m^3, 7 hrs/day, on days 6 to 15 of gestation. At 147 mg/m^3, the only effects were significant increases in delayed skull ossification and wavy ribs (Schwetz, et al., 1974).

Table 1. Hepatocellular Carcinoma Incidence in Mice[a]

	Controls		Low Dose	High Dose
	Colony	Matched		
Male	5/77 (6%)	1/18 (6%)	138 mg/kg 18/50 (30%)	277 mg/kg 44/45 (98%)
Female	1/80 (1%)	0/20 (0%)	238 mg/kg 36/45 (80%)	477 mg/kg 39/41 (95%)

Table 2. Statistically Significant Tumor Incidence in Rats[a]

	Males			
	Controls		Low Dose	High Dose
	Colony	Matched		
Kidney epithelial tumors/animals	0/99	0/19	90 mg/kg 4/50 (8%)	180/mg/kg 12/50 (24%)
P value	0.0000	0.0016		

[a]Source: National Cancer Institute, 1976.

D. Other Reproductive Effects

Pertinent data could not be located in the available literature.

E. Chronic Toxicity

The NIOSH Criteria Document (1974) tabulates data on the effect of chronic chloroform exposure in humans. The primary target organs appear to be the liver and kidneys, with some signs of neurological disorders. These effects have been documented only with occupational exposures.

With the exception of the possible relationship to cancer (Section IV.A), chronic toxic effects in humans, attributable to ambient levels of chloroform, have not been documented.

The chronic effects of chloroform in experimental mammals is similar to the effects seen in humans: liver necrosis and kidney degeneration (Torkelson, et al., 1976; U.S. EPA, 1979a).

F. Other Relevant Information

Ethanol pretreatment of mice reportedly enhances the toxic effects of chloroform on the liver (Kutob and Plaa, 1961); as does high fat and low protein diets (Van Oettingen, 1964; McLean, 1970). These data were generated using experimental mammals.

V. AQUATIC TOXICITY

A. Acute Toxicity

Bentley, et al. (1975) observed the 96-hour LC_{50} values for rainbow trout, (Salmo gairdneri), of 43,800 and 66,800 µg/l and for bluegills (Lepomis macrochirus), 100,000 to 115,000 µg/l, all in static tests. A 48-hour static test with Daphnia magna resulted in an LC_{50} of 28,900 µg/l (U.S. EPA 1979a). The observed 96-hour LC_{50} for the pink shrimp (Panaeus duorarum) is 81,500 µg/l. (Bentley, et al., 1975).

B. Chronic Toxicity

The chronic effects of chloroform on Daphnia magna were determined using flow-through methods with measured concentrations. The chronic effect level was 2,546 µg/l (U.S. EPA, 1979a). No other chronic data were available.

C. Plant Effects

Pertinent information could not be located in the available literature concerning acute chronic toxicity of chloroform to plants.

D. Residues

In the only residue study reported, the bluegill (Lepomis macrochirus) bioconcentrated chloroform six times after a 14-day exposure (U.S. EPA, 1979a). The tissue half-life was less than one day.

VI. EXISTING GUIDELINES AND STANDARDS

Both the human health and aquatic criteria derived by U.S. EPA (1979a), which are summarized below, are being reviewed; therefore, there is a possibility that these criteria may be changed.

A. Human

Based on the NCI mice data, and using the "one-hit" model, the EPA (1979a) has estimated levels of chloroform in ambient water which will result in specified risk levels of human cancer:

Exposure Assumption (per day)	Risk Levels and Corresponding Criteria			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish.	0	0.021 µg/l	0.21 µg/l	2.1 µg/l
Consumption of fish shellfish only.	0	0.175 µg/l	1.75 µg/l	17.5 µg/l

The above risks assume that drinking water treatment and distribution will have no impact on the chloroform concentration.

The NIOSH time-weighted average exposure criterion for chloroform is 2 ppm or 9.8 mg/m^3.

The FDA prohibits the use of chloroform in drugs, cosmetics, or food contact material (14 FR 15026, 15029 April 9, 1976).

Refer to the Halomethane Hazard Profile for discussion of criterion derivation (U.S. EPA, 1979b).

B. Aquatic

For chloroform, the draft criterion to protect freshwater aquatic life, based on chronic invertebrate toxicity, is 500 µg/l as a 24-hour average and the concentration should not (based on acute effects) exceed 1,200 µg/l at any time (U.S. EPA, 1979a). To protect saltwater aquatic life, the concentration of chloroform should not exceed 620 µg/l as a 24-hour average and the concentration should not exceed 1,400 µg/l at anytime (U.S. EPA, 1979a). These were calculated from an experiment on a marine invertebrate.

CHLOROFORM

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No. 48

Chloromethane

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

CHLOROMETHANE

SUMMARY

Chloromethane is toxic to humans by its action on the central nervous system. In acute toxicity, symptoms consist of blurring vision, headache, vertigo, loss of coordination, slurring of speech, staggering, mental confusion, nausea, and vomiting. Information is not available on chronic toxicity, teratogenicity, or carcinogenicity. Chloromethane is highly mutagenic to the bacteria, Salmonella typhimurium.

Only three toxicity tests have been conducted on three species of fish yielding acute values ranging from 147,000 to 300,000 µg/l. Tests on aquatic invertebrates or plants have not been conducted.

CHLOROMETHANE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Halomethanes (U.S. EPA, 1979a).

Chloromethane (CH_3Cl; methyl chloride; molecular weight 50.49) is a colorless, flammable, almost odorless gas at room temperature and pressure (Windholz, 1976). Chloromethane has a melting point of -97.7°C, a boiling point of -24.2°C, a specific gravity of 0.973 g/ml at -10°C, and a water solubility of 5.38×10^6 µg/l. It is used as a refrigerant, a methylating agent, a dewaxing agent, and catalytic solvent in synthetic rubber production (MacDonald, 1964). However, its primary use is as a chemical intermediate (Natl. Acad. Sci., 1978). Chloromethane is released to the environment by manufacturing and use emissions, by synthesis during chlorination of drinking water and municipal sewage, and by natural synthesis, with the oceans as the primary site (Lovelock, 1975). For additional information regarding the halomethanes as a class, the reader is referred to the Hazard Profile on Halomethanes (U.S. EPA, 1979b).

II. EXPOSURE

A. Water

The U.S. EPA (1975) has identified chloromethane qualitatively in finished drinking waters in the U.S. However, there are no data on its concentration in drinking water, raw water, or waste-water (U.S. EPA, 1979a), probably because it is more reactive than other chlorinated methanes (Natl. Acad. Sci., 1978).

B. Food

There is no information on the presence of chloromethane in food. There is no bioconcentration factor for chloromethane (U.S. EPA, 1979a).

C. Inhalation

Saltwater atmospheric background concentrations of chlorometnane averaging about 0.0025 mg/m^3 have been reported (Grimsrud and Rasmussen, 1975, Singh, et al. 1977). This is higher than reported average continental background and urban levels and suggests that the oceans are a major source of global chloromethane (National Acad. Sci., 1978). Localized sources, such as burning of tobacco or other combustion processes, may produce high indoor-air concentrations of chloromethane (up to 0.04 mg/m^3) (Natl. Acad. Sci., 1978). Chloromethane is the predominant halomethane in indoor air, and is generally in concentrations two to ten times ambient background levels.

III. PHARMACOKINETICS

A. Absorption

Chloromethane is absorbed readily via the lungs, and to a less significant extent via the skin. Poisonings involving gastrointestinal absorption have not been reported (Natl. Acad. Sci., 1977; Davis, et al., 1977).

B. Distribution

Uptake of chloromethane by the blood is rapid but results in only moderate blood levels with continued exposure. Signs and pathology of intoxications suggest

wide tissue (blood, nervous tissue, liver, and kidney) distribution of absorbed chloromethane (Natl. Acad. Sci., 1978).

C. Metabolism

Decomposition and sequestration of chloromethane result primarily by reaction with sulfhydryl groups in intracellular enzymes and proteins (Natl. Acad. Sci., 1977).

IV. EFFECTS

A. Carcinogenicity

Pertinent information could not be located in the available literature.

B. Mutagenicity

Simmon and coworkers (1977) reported that chloromethane was mutagenic to Salmonella tryphimurium strain TA 100 when assayed in a dessicator whose atmosphere contained the test compound. Metabolic activation was not required, and the number of revertants per plate was directly dose-related. Also, Andrews, et al. (1976) have demonstrated that chloromethane was mutagenic to S. typhimurium strain TA1535 in the presence and absence of added liver homogenate preparations.

C. Teratogenicity and Other Reproductive Effects

Information on positive evidence of teratogenisis or other reproductive effects was not available in the literature.

D. Chronic Toxicity

Under prolonged exposures to chloromethane (duration not specified) increased mucous flow and reduced mucosta-

tic effect of other agents (e.g., nitrogen oxides) were noted in cats (Weissbecker, et al., 1971).

E. Other Relevant Information

In acute human intoxication, chloromethane produces central nervous system depression, and systemic poisoning cases have also involved hepatic and renal injury (Hansen, er al., 1953; Spevac, et al., 1976).

V. AQUATIC TOXICITY

A. Acute Toxicity

A single 96-hour static renewal test serves as the only acute study for freshwater providing an adjusted LC_{50} value of 550,000 µg/l for the bluegill sunfish (Lepomis macrochirus). (Dawson, et al., 1977). Studies on freshwater invertebrates were not found. For the marine fish, the tidewater silversides (Menidia beryllina), a 96-hour static renewal assayed provided an LC_{50} value of 270,000 µg/l (Dawson, et al., 1977). Acute studies on marine invertebrates were not found.

B. Chronic Toxicity

In a review of the available literature, chronic testing with chloromethane has not been reported.

C. Plant Effects

Pertinent information could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human nor the aquatic criteria derived by U.S. EPA, 1979a, which are summarized below, have gone

through the process of public review; therefore, there is a possibly that these criteria may be changed.

A. Human

OSHA (1976) has established the maximum acceptable time-weighted average air concentrations for daily eight-hour occupational exposure at 210 mg/m^3. The U.S. EPA (1979a) Draft Water Quality Criteria for Chloromethane is 2 µg/l. Refer to the Halomethanes Hazard Profile for discussion of criteria derivation (U.S. EPA, 1979b).

B. Aquatic

Criterion recommended to protect freshwater organisms have been drafted as 7,000 µg/l, not to exceed 16,000 µg/l for a 24-hour average concentration. For marine life, the criterion has been drafted as 3,700 µg/l, not to exceed 8,400 µg/l as a 24-hour average concentration.

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No. 49

2-Chloronaphthalene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

2-CHLORONAPHTHALENE

SUMMARY

Monochlorinated naphthalenes are relatively insoluble in water. They can be slowly degraded by bacteria and are subject to photochemical decomposition. Monochlorinated naphthalenes appear to bioconcentrate in plants and animals exposed to the substances. 2-Chloronaphthalene has been identified as a pollutant in a variety of industries.

No information was located on the carcinogenicity, mutagenicity, or teratogenicity of 2-chloronaphthalene or other monochlorinated naphthalenes. The metabolism of some chlorinated naphthalenes, however, proceeds through an epoxide mechanism. If an epoxide is formed as an intermediate in the metabolism of 2-chloronaphthalene, it could react with cellular macromolecules possibly resulting in cytotoxicity, mutagenicity, oncogenicity, or other effects.

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Chlorinated Naphthalenes (U.S. EPA, 1979b).

2-Chloronaphthalene ($C_{10}H_7Cl$; molecular weight 162) is a crystalline solid with a melting point of 61°C and a boiling point of 256°C. Its density at 16°C is 1.27. It is insoluble in water and soluble in many organic solvents (Weast; 1972 and Hardie, 1964).

A review of the production range (includes importation) statistics for 2-chloronaphthalene (CAS. No. 91-58-7) which is listed in the inital TSCA Inventory (1979a) has shown that between 1,000 and 9,000 pounds of this chemical were produced/imported in 1977.*/

Monochloronaphthalenes and mixtures of mono- and dichloronaphthalenes have been used for chemical-resistant gauge fluids and instrument seals, as heat exchange fluids, high-boiling specialty solvents (e.g., for solution polymerization), color dispersions, engine crankcase additives to dissolve sludges and gums, and as ingredients in motor tuneup compounds. Monochloronaphthalene was formerly used as a wood preservative (Dressler, 1979).

II. EXPOSURE

A. Environmental Fate

Polychlorinated naphthalenes do not occur naturally in the environment. Potential environmental accumulation can occur around points of manufacture of the compounds or products containing them, near sites of disposal of polychorinated naphthalene-containing wastes, and, because polychlorinated

*/ This production range information does not include any production/importation data claimed as confidential by the person(s) reporting for the TSCA inventory, nor does it include any information which would compromise Confidential Business Information. The data submitted for the TSCA Inventory, including production range information, are subject to the limitations contained in the Inventory Reporting Regulations (40 CFR 710).

biphenyls (PCBs) are to some extent contaminated by polychlorinated naphthalenes (Vos et al. 1970; Bowes et al. 1975) near sites of heavy PCB contamination.

Because polychlorinated naphthalenes are relatively insoluble in water, they are not expected to migrate far from their point of disposition. The use of mono- and dichlorinated naphthalenes as an engine oil additive and as a polymerization solvent in the fabric industry suggests possible contamination of soil or water.

Walker and Wiltshire (1955) found that soil bacteria when first grown on naphthalene could also grow on 1-chloronaphthalene, producing a diol and chlorosalicylic acid. Canonica et al. (1957) found similar results for 2-chloronaphthalene. Okey and Bogan (1965) studied the utilization of chlorinated substrates by activated sludge and found that naphthalene was degraded at a fairly rapid rate, while 1-and 2-chloronaphthalenes were handled more slowly.

Ruzo et al. (1975) studied the photodegradation of 2-chloronaphthalene in methanol. The major reaction pathways seen were dechlorination and dimerization. Jaffe and Orchin (1966) indicated that any 2-chloronaphthalene present at the surface of water could be degraded by sunlight to naphthalene. In the aquatic environment, 2-chloronaphthalene can exist as a surface film, be adsorbed by sediments, or accumulated by biota.

B. Bioconcentration

Monochlorinated naphthalenes appear to bioconcentrate in the aquatic environment. Adult grass shrimp (Palaemonetes pugio) were exposed to a mixture of mono- and dichloro naphthalenes for 15 days. The concentration of chloronaphthalenes detected in the shrimp was 63 times that of the experimental environment. When removed from the contaminated environment, however, the concentration in the shrimp returned to virtually zero within 5 days (Green and Neff, 1977).

Erickson et al. (1978a) reported a higher relative bioconcentration of the lower chlorinated naphthalenes in the fruit of apple trees grown on contaminated soil. The soil was found to have a polychlorinated naphthalene level of 190 ug/kg of which 1.6 ug/kg consisted of monochloronaphthalenes. While the apples grown on this soil had only 90 ug/kg of polychlorinated naphthalenes, the level of monochloronaphthalene was 62 ug/kg.

C. Environmental Occurrence

2-Chloronaphthalene has been identified as a pollutant in a variety of industries, e.g. organic chemical, rubber, power generation, and foundries (U.S. EPA, 1979c).

Chlorinated naphthalenes have been found more consistently in air and soil samples than in associated rivers and streams (Erickson et al., 1978b). The air samples contained mainly the mono-, di- and trichlorinated naphthalenes, while soil contained mostly the tri-, tetra- and pentachlorinated derivatives.

To date polychlorinated naphthalenes have not been identified in either drinking water or market basket food. The Food and Drug Administration has had polychlorinated naphthalene

monitoring capability for foods since 1970, but has not reported their occurrence in food (U.S. EPA, 1975).

III. PHARMACOKINETICS

Ruzo et al. (1976b) reported the presence of 2-chloronaphthalene in the brain, kidney, and liver of pigs six hours after injection. Small concentrations of 3-chloro-2-naphthol, a metabolite , were seen in the kidney and liver with large amounts occurring in the urine and bile. The metabolism of some chlorinated napthalenes proceeds through an epoxide mechanism (Ruzo et al. 1975, 1976ab; Chu et al., 1977ab).

IV. HEALTH EFFECTS

A. Teratogenicity, Mutagenicity, and Carcinogenicity

No information was located on the carcinogenicity, mutagenicity, or teratogenicity of polychlorinated naphthalenes.

If an epoxide is formed as an intermediate in the metabolism of 2-chloronaphthalene, it could react with cellular macromolecules. Binding might occur with protein, RNA, and DNA resulting in possible cytotoxicity, mutagenicity, oncogenicity, or other effects (Garner, 1976; Heidelberger, 1973; Wyndham and Safe, 1978).

B. Other Toxity

In man, the first disease recognized as being associated with occupational exposure to higher polychlorinated naphthalenes was chloracne. Occurrence of this disease was associated with the manufacture or use of polychloronaphthalene-treated electrical cables. Kleinfeld et al. (1972) noted that workers at

an electric coil manufacturing plant had no cases of chloracne while using a mono- and dichloronaphthalene mixture. When a tetra-/pentachlorinated naphthalene mixture was substituted for the original mixture, 56 of the 59 potentially exposed workers developed chloracne within a "short" time.

The lower chlorinated naphthalenes appear to have low acute toxicity. Mixtures of mono-/dichloronaphthalenes and tri-/tetra-chloronaphthalenes at 500 mg/g in a mineral oil suspension applied to the skin of the human ear caused no response over a 30-day period. A mixture of penta-/hexachloronaphthalenes given under the same conditions caused chloroacne (Shelley and Kligman, 1957).

The oral LD50 for rats and mice is 2078 mg/kg and 886 mg/kg respectively (NIOSH, 1978). No mortality or illness was reported in rabbits given 500 mg/kg orally (Cornish and Block, 1958).

V. AQUATIC EFFECTS

The LC50 (ppb) of a mixture of 60% mono- and 40% dichloro-naphthalenes in grass shrimp (Palaemonetes pugio)is as follows:

	72-hr	96-hr
post larval stage	-	449
adult	370	325

(Green and Neff, 1977)

VI. EXISTING GUIDELINES

There are no existing guidelines for 2-chloronaphthalene.

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No. 50

2-Chlorophenol

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

2-CHLOROPHENOL

SUMMARY

Insufficient data exist to indicate that 2-chlorophenol is a carcinogenic agent. 2-Chlorophenol appears to act as a nonspecific irritant in promoting tumors in skin painting studies. No information is available on mutagenicity, teratogenicity, or subacute and chronic toxicity. 2-Chlorophenol is a weak uncoupler of oxidative phosphorylation and a convulsant.

2-Chlorophenol is acutely toxic to freshwater fish at concentrations ranging from 6,590 to 20,170 µg/l. No marine studies are available. Concentrations greater than 60 µg/l have been reported to taint cooked rainbow trout flesh in flavor impairment studies.

I. INTRODUCTION

This profile is based primarily on the Ambient Water Quality Criteria Document for 2-Chlorophenol (U.S. EPA, 1979).

2-Chlorophenol (ortho-chlorophenol) is a liquid having the empirical formula C_6H_5Cl (molecular weight: 128.56). It has the following physical/chemical properties (Rodd, 1954; Judson and Kilpatrick, 1949; Sax, 1975; Stecher, 1968; Henshaw, 1971):

Melting Point:	8.7°C
Boiling Point Range:	175-176°C
Vapor Pressure:	1 mm Hg at 12.1°C
Solubility:	Slightly soluble (1g/l) in water at 25°C and neutral pH

2-Chlorophenol is a commercially produced chemical used as an intermediate in the production of higher chlorophenols and phenolic resins and has been utilized in a process for extracting sulfur and nitrogen compounds from coal (U.S. EPA, 1979).

2-Chlorophenol undergoes photolysis in aqueous solutions as a result of UV irradiaton (Omura and Matsuura, 1971; Joschek and Miller, 1966). Laboratory studies suggest that microbial oxidation could be a degradation route for 2-chlorophenol (Loos, et al., 1966; Sidwell, 1971; Nachtigall and Butler, 1974). However, studies performed by Ettinger and Ruchhoft (1950) on the persistency of 2-chlorophenol in sewage and polluted river water indicated that the removal of monochlorophenols requires the presence of an adapted microflora.

II. EXPOSURE

A. Water

The generation of waste from the commercial production and use of 2-chlorophenol (U.S. EPA, 1979) and the inadvertent synthesis of 2-chlorophenol due to chlorination of water contaminated with phenol (Aly, 1968: Barnhart and Campbell, 1972; Jolley, 1973; Jolley, et al., 1975) are potential sources of contamination of water with 2-chlorophenol. However, no data regarding 2-chlorophenol concentrations in finished drinking water are available (U.S. EPA, 1979).

B. Food

Information on levels of 2-chlorophenol in foods is not available. Any contamination of foods is probably indirect as a result of use and subsequent metabolism of phenoxyalkanoic herbicides (U.S. EPA, 1979). Although residues of 2,4-dichlorophenol were found in tissues of animals fed 2,4-D and nemacide containing food (Clark, et al. 1975); Sherman, et al. 1972), no evidences were cited to indicate the presence of 2-chlorophenol; moreover, there was no contamination of 2-chlorophenol in milk and cream obtained from cows fed 2,4-D treated food (Bjerke, et al. 1972).

The potential for airborne exposure to 2-chlorophenol in the general environment, excluding occupational exposure, has not been reported (U.S. EPA, 1979).

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for 2-chlorophenol and the edible portion of fish and shellfish consumed by Americans at

490. This estimate is based on measured steady state bioconcentration studies in bluegills.

C. Inhalation

Pertinent data regarding concentrations of 2-chlorophenol in ambient air could not be found in the available literature.

III. PHARMACOKINETICS

A. Absorption

Data dealing directly with the absorption of 2-chlorophenol by humans and experimental animals has not been found. Chlorophenol compounds are generally considered to be readily absorbed, as would be expected from their high lipid solubility and low degree of ionization at physiological pH (Doedens, 1963; Farquharson, et al., 1958). Toxicity studies indicate that 2-chlorophenol is absorbed through the skin.

B. Distribution

Pertinent data regarding tissue distribution of 2-chlorophenol was not located in the available literature.

C. Metabolism

Data regarding the metabolism of 2-chlorophenol in humans was not available (U.S. EPA, 1979). Based on experimental work in two species, it appears that the metabolism of 2-chlorophenol in mammals is similar to that of phenol in regard to the formation and excretion of sulfate and glucuronide conjugates (Von Oettingen, 1949; Lindsay-Smith, et al. 1972) Conversion of chlorobenzene to monochlorophenols, including 2-chlorophenol, has been shown in vitro with rat

liver (Selander, et al. 1975) and in vivo, with rabbits (Lindsay-Smith, et al. 1972).

D. Excretion

Studies on rate and route of excretion for 2-chlorophenol in humans were not available. Dogs excreted 87 percent of administered 2-chlorophenol in the urine as sulfate and glucuronide conjugates (Von Oettingen, 1949). The same metabolites were found in the urine of rabbits after administration of chlorobenzene (Lindsay-Smith, et al. 1972); however, out of the total free and conjugated chlorophenols only 6 percent were present as 2-chlorophenol.

IV. EFFECTS

A. Carcinogenicity

Insufficient data exist to indicate that 2-chlorophenol is a carcinogen. In the only study found (Boutwell and Bosch, 1959), 2-chlorophenol promoted skin cancer in mice after initiation with dimethylbenzanthracene and when repeatedly applied at a concentrations high enough to damage the skin. 2-Chlorophenol was not carcinogenic when applied repeatedly without initiation with dimethylbenzanthracene, but did induce a high incidence of papillomas and no carcinomas.

Information regarding mutagenicity, teratogenicity, other reproductive effects and chronic toxicity could not be found in the available literature.

F. Other Relevant Information

2-Chlorophenol is a weak uncoupler of oxidative phosphorylation (Mitsuda, et al., 1963) and a convulsant (Farquharson, et al., 1958; Angel and Rogers, 1972).

V. AQUATIC TOXICITY

A. Acute Toxicity

Acute studies on four species of fish have produced 96-hour static LC_{50} values ranging from 6,590 µg/l in the bluegill (Lepomis macrochirus) (U.S. EPA, 1978) to 20,170 µg/l to the guppy (Poecilia reticulatus). Juvenile bluegills were more sensitive in a static renewal assay with an LC_{50} value of 8,400 µg/l. The fathead minnow (Pimephales promelas) was the only freshwater fish tested in a flow through system and gave an LC_{50} value of 12,380 µg/l. Daphnia magna has been found to have 48-hour static LC_{50} values of 2,580 µg/l and 7,430 µg/l. No data concerning the effects of 2-chlorophenol to marine fish or invertebrates are available.

B. Chronic Toxicity

Effects were not obtained in a chronic embryo-larval test of 2-chlorophenol at concentrations as high as 1,950 µg/l for the freshwater fathead minnow. Additional chronic studies are not available.

C. Plant Effects

The only plant assay available provides an effective concentration of 500,000 µg/l in chlorophyll reduction in the algae, Chlorella pyrenoidosa.

D. Residues

A measured bioconcentration factor of 214 has been obtained for the bluegill. The half-life was less than one day, indicating a rapid depuration rate for 2-chlorophenol.

E. Miscellaneous

Flavor impairment of the edible portion of fish exposed to 2-chlorophenol has been reported. The highest concentration of 2-chlorophenol in the exposure water which would not impair the flavor of cooked rainbow trout (Salmo gairdneri) has been estimated at 60 µg/l Shumway and Palensky, 1973).

VI. EXISTING GUIDLINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria may be changed.

A. Human

Based on the prevention of adverse organoleptic effects, the U.S. EPA (1979) draft interim criterion recommended for 2-chlorophenol in ambient water is 0.3 µg/l. There are no other standards or guidelines for exposure to 2-chlorophenol.

B. Aquatic

Based on the tainting of fish, the draft criterion to protect freshwater organisms from 2-chlorophenol is 60 µg/l as a 24-hour average, not to exceed 180. µg/l at any time. No criterion was derived for marine life (U.S. EPA, 1979).

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SJ-45-01

No. 51

Chromium

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

October 30, 1980

DISCLAIMER

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CHROMIUM

Summary

Hexavalent chromium (CrVI), at low concentrations in water, has a deleterious effect on the growth of fish, aquatic invertebrates, and certain species of algae. For the most sensitive aquatic species, Daphnia magna, a final chronic no-effect level of less than 10 ug/l has been derived by the U.S. EPA. For trivalent Cr(CrIII) toxic effects are more pronounced in soft than in hard water; chronic no-effect levels are derived as a function of water hardness.

Several hexavalent Cr compounds have produced tumors in animal studies. Human epidemiology studies indicate a possible etiology of Cr exposure in the production of lung tumors in occupationally exposed workers. Trivalent Cr has not shown carcinogenic effects.

Mutagenic effects, including cytogenetic effects in exposed workers, have been reported for hexavalent chromium compounds. Trivalent chromium compounds were not mutagenic in the Ames bacterial assay. Teratogenic effects of chromium have been reported in a single study and have not been confirmed.

Impairment of pulmonary function has been reported in chrome electroplating workers subject to chronic chromium exposure. However, exposure to multiple agents complicates the interpretation of this finding.

CHROMIUM

I. INTRODUCTION

This profile is in large part based on the Ambient Water Quality Criteria Document for Chromium (U.S. EPA, 1980).

Chromium (Cr) is a steel gray, lustrous, hard metal that melts at 1857 ± 20°C, boils at 2672°C, and has a specific gravity of 7.18 to 7.20 at 20°C (Weast, 1974). Cr compounds exist in a variety of oxidation states; the most commonly occurring are those of the trivalent and hexavalent states. Physical properties of some Cr compounds are summarized in Table 1.

Cr compounds are utilized in the paint and dye industries as pigments and mordants, in metallurgy for the production of stainless steel and other alloys, in the chrome tanning of leather goods, in the production of high melting refractory materials, and for chrome plating.

Hexavalent Cr compounds are relatively water soluble and are readily reduced to more stable and insoluble trivalent forms by reaction with organic reducing matter. Trivalent chromium forms stable hexacoordinate complexes with a great variety of ligands (water, ammonia, urea, halides, sulfates, ethylene diamine, organic acids). In neutral and basic solutions, trivalent Cr may form polynuclear bridge compounds that eventually precipitate. Hexavalent Cr exists in solution as a component of an anion (hydrochromate, chromate, or dichromate) and does not precipitate from alkaline solution.

The specific anionic form of hexavalent Cr is dependent on pH - in the acid range hydrochromate predominates, while in the alkaline range the predominant form is chromate (Trama and Benoit, 1960). Cr VI occurs naturally in alkaline soft waters (Robertson, 1975) and in aerated sea water (Fukai, 1967; Cutshall et. al., 1965; Emerson et. al., 1979). The oxidation of CR III is expected to occur on energetic grounds (Carlin, 1965; U.S. EPA, 1977). In fact, however, oxidation takes place only very slowly in natural waters, except in the presence of MnO_2 (Schroeder and Lee, 1975; U.S. EPA, 1978). Under laboratory conditions oxidation does occur (Schroeder and Lee, 1975; Stephens, 1977). In contrast, the reduction of Cr VI to Cr III occurs rapidly in lake waters (Schroeder and Lee, 1975).

It seems probable that in most waters, especially under neutral or slightly acid conditions, Cr VI is reduced to Cr III, the hydroxy complexes of which precipitate out and/or are absorbed onto clays and other soil elements (N.A.S., 1974; U.S. EPA, 1978).

Since Cr is an element, it persists indefinitely in the environment in some form. Trivalent Cr compounds are more likely to accumulate in sediments, while hexavalent forms remain soluble and dissipate with the water flow (U.S. EPA, 1980).

II. EXPOSURE

Large amounts of hexavalent Cr are produced and utilized

in industry, primarily as chromates and dichromates (U.S. EPA, 1980). Industrial processes consumed 320,000 metric tons of Cr metal alone in 1972.

Much of the detectable chromium in air and water is presumably derived from industrial processes. Levels of total Cr in the air exceeding 0.10 mg/m^3 were reported from 59 of 186 urban areas examined (U.S. EPA, 1973). Air levels in non-urban areas generally fall below detection limits. Mean concentration of Cr in 1577 samples of surface water was determined as 9.7 ug/l (Kopp, 1969). Cr is naturally distributed in the continental crust at an average concentration of 125 mg/kg (N.A.S., 1974).

Based on available monitoring data, the U.S. EPA (1980) has estimated the uptake of Cr by adult humans from air, water and food:

Source	Uptake ug/day
Atmosphere	1
Water	20
Food Supply	50-100
	121

A different estimate for self-selected diets was 280ug/day (NAS, 1974). It is often stated that the American diet may be marginally deficient in Cr. Since a MDR has not yet been established (Mertz, 1978), and since absorption factors (see below) are as yet poorly understood, this statement is open to question.

Table 1. Physical Properties of Typical Chromium Compounds

Compound	Formula	Appearance	Crystal system and space group	Density (g/cm^3)	Melting point (°C)	Boiling point (°C)	Solubility
Oxidation state 0							
Chromium carbonyl	$(Cr(CO)_6$	Colorless crystals	Orthorhombic, C^9_{2r}	1.77_{18}	150 (decomposed) (sealed tube)	151 (decomposed)	Slightly soluble in CCl_4; insoluble in H_2O, $(C_2H_5)_2O$, C_2H_5OH, C_6H_6
Dibenzene chromium(0)	$(C_6H_6)_2Cr$	Brown crystals	Cubic, Pa_3	1.519	284-285	Sublimes 150 (vacuum)	Insoluble in H_2O; soluble in C_6H_6
Oxidation state + 1							
bis(biphenyl)-chromium (I) iodide	$(C_6H_5C_6H_5)_2CrI$	Orange plates		1.617_{16}	178	Decomposes	Soluble in C_2H_5OH, C_5H_5N
Oxidation state + 2							
Chromous acetate	$Cr_2(C_2H_3O_2)_4 \cdot 2H_2O$	Red crystals	Monoclinic, C2/c	1.79			Slightly soluble in H_2O; soluble in solids
Chromous chloride	$CrCl_2$	White crystals	Tetragonal, D^{14}_{4h}	2.93	815	1120	Soluble in H_2O to blue solution, absorbs O_2
Chromous ammonium sulfate	$CrSO_4 \cdot (NH_4)_2SO_4 \cdot 6H_2O$	Blue crystals	Monoclinic, C^5_{2h}				Soluble in H_2O, absorbs O_2
Oxidation state + 3							
Chromic chloride	$CrCl_3$	Bright purple plates	Hexagonal, D^{3or5}_3	2.87_{25}	Sublimes	885	Insoluble in H_2O, soluble in presence of Cr^{2+}
Chromic acetyl-acetonate	$Cr(CH_3COCHCOCH_3)_3$	Red-violet crystals	Monoclinic	1.34	208	345	Insoluble in H_2O; soluble in C_6H_6
Chromic potassium sulfate (chrome alum)	$KCr(SO_4)_2 \cdot 12H_2O$	Deep purple crystals	Cubic, A^6_n	1.826_{15}	89 (incongruent)		Soluble in H_2O
Chromic chloride hexahydrate	$(Cr(H_2O)_4Cl_2)Cl \cdot 2H_2O$	Bright green crystals	Triclinic or monoclinic	1.835_{25}	95		Soluble in H_2O, green solution turning green-violet
Chromic chloride hexahydrate	$(Cr(H_2O)_6)Cl_3$	Violet crystals	Rhombohedral, D^6_{3d}		90		Soluble in H_2O, violet solution turning green-violet

Compound	Formula	Appearance	Crystal system and space group	Density (g/cm^3)	Melting point (°C)	Boiling point (°C)	Solubility
Chromic oxide	Cr_2O_3	Green powder or crystals	Rhombohedral, D^6_{3d}	5.22_{25}	2435	ca. 3000	Insoluble
Oxidation state + 4							
Chromium (IV) oxide	CrO_2	Dark Brown or black powder	Tetragonal, D^{14}_{4h}	4.98 (calculated)		Decomposes to Cr_2O_3	Soluble in acids to Cr^{3+} and Cr^{6+}
Chromium(IV) chloride	$CrCl_4$		Stable only at high temp.			830	
Oxidation state + 5							
Barium chromate(IV)	$Ba_3(CrO_4)_2$	Black-green crystals	Same as $Ca_3(PO_4)_2$				Slightly decomposes in H_2O; soluble in dilute acids to Cr^{3+} and Cr^{6+}
Oxidation state + 6							
Chromium(VI) oxide	CrO_3	Ruby-red crystals	Orthorhombic, C^{16}_{2v}	2.7_{25}	197	Decomposes	Very soluble in H_2O; soluble in CH_3COCH_3, $(CH_2CO)_2O$
Chromyl chloride	CrO_2Cl_2	Cherry-red liquid		1.9145_{25}	-96.5	115.8	Insoluble in H_2O; hydrolyzes; Soluble in CS_2, CCl_4
Ammonium dichromate	$(NH_4)_2Cr_2O_7$	Red-orange crystals	Monoclinic	2.155_{25}	Decomposes		Soluble in H_2O
Potassium dichromate	$K_2Cr_2O_7$	Orange-red crystals	Triclinic	2.676_{25}	398	Decomposes	Soluble in H_2O
Sodium dichromate	$Na_2Cr_2O_7 \cdot 2H_2O$	Orange-red crystals	Monoclinic	1.348_{25}	84.6 (incongruent)	Decomposes	Very soluble in H_2O
Potassium chromate	K_2CrO_4	Yellow crystals	Orthorhombic	2.732_{18}	971		Soluble in H_2O
Sodium chromate	Na_2CrO_4	Yellow crystals	Orthorhombic, D^{17}_{2h}	2.723_{25}	792		Soluble in H_2O
Potassium chlorochromate	$KCrO_3Cl$	Orange crystals	Monoclinic	2.497_{39}	Decomposes		Soluble in H_2O, hydrolyzes
Silver chromate	Ag_2CrO_4	Maroon crystals	Monoclinic	5.625_{25}			Very slightly soluble in H_2O; soluble in dilute acids
Barium chromate	$BaCrO_4$	Main yellow solid	Orthorhombic	4.498_{25}	Decomposes		Very slightly soluble in H_2O; soluble in strong acids

Compound	Formula	Appearance	Crystal system and space group	Density (g/cm^3)	Melting point (^oC)	Boiling point (^oC)	Solubility
Strontium chromate	$SrCrO_4$	Yellow solid	Monoclinic, C_{2h}^5	3.895_{15}	Decomposes		Slightly soluble in H_2O; soluble in dilute acids
Lead chromate	$PbCrO_4$	Yellow solid Orange solid	Orthorhombic Monoclinic, C_{2h}^5	6.12_{15}	844		Practically insoluble in H_2O; soluble in strong acids
		Red solid	Tetragonal				

Source: Adapted from U.S. EPA, 1978.

The U.S. EPA (1980) has derived a bioconcentration factor (BCF) of 11 for chromium.

III. PHARMACOKINETICS

A. Absorption

The efficiency of Cr absorption by the gastrointestinal tract is a function of the oxidation and chemical forms of the compound and the presence of other dietary constituents, and poorly understood intestinal epithelial barriers (U.S. EPA, 1980; Mertz, 1978). Oral administration of trivalent Cr results in little absorption. In order to be assimilated chromium must be present in the form of an organic complex with nicotinic acid termed glucose tolerance factor (GTF) (Mertz, 1969; 1971; 1978). Inorganic Cr is poorly assimilated (a few per cent) (Mertz, 1969; 1971). Cr from animal sources is much better utilized than that from vegetables, in which it may occur in high concentrations (Mertz, 1978). Dermal absorption of Cr does not contribute greatly to total body load, except in situations where toxic external concentrations have produced ulceration (U.S. EPA, 1980). Pulmonary exposure to Cr, which can be significant in some industrial situations, leads to prolonged retention at this site (Baetjer, et al. 1959). Under most conditions, however, the contribution of the inhalation route to total absorbed Cr is small (U.S. EPA, 1980).

B. Distribution

Analysis of the metabolism and distribution of Cr

is complicated by the fact that the methods available for the estimation of Cr at low levels do not adequately distinguish between its different forms (U.S. EPA 1980; 1978). In addition, difficulties of interpretation arise from the fact that cellular constituents reduce Cr to the trivalent form (Petrilli and DeFlora 1978; Nakamuro 1978).

Absorbed Cr is primarily transported bound to siderophilin, a metal transport protein which predominantly binds iron.

The organ distribution of Cr is highly dependent on the chemical form administered. For instance, while trivalent Cr does not extensively cross the placental barrier, when administered to pregnant rats in complexed form (GTF), it is taken up by the fetus. The highest concentrations of Cr accumulate in skin, lung, muscle and fat (Mertz 1969, Casarett and Doull, 1979). Pulmonary Cr arises from inhalation, and does not equilibrate with other body stores. Cr concentration in tissues other than lungs decline somewhat with age (Mertz 1969).

Hexavalent Cr is reduced to the trivalent form in skin. In the blood little hexavalent Cr is detected. The reticuloendothelial system, liver, spleen, testis and bone marrow have an affinity for trivalent Cr, (Mertz 1969); chromates are bound largely to red blood cells (Mertz 1969). Inside cells, about half of the Cr is in the nucleus.

C. Metabolism

Analysis of chromium metabolism is complicated by the extensive binding of chromium to tissue components

(enzymes, proteins, nucleic acids) and by the inability of analytical methods to distinguish between the different forms of chromium (U.S. EPA, 1978; 1980).

Studies of the kinetics of radiochromium distribution in humans indicated three major accumulation and clearance components (Lim, 1978). Animal studies with radioactive chromium trichloride injected intravenously showed that heart, lung, pancreas, and brain retain only 10 to 31 percent of their initial radioactivity after four days. Spleen, kidney, testis and epididymis concentrate chromium (Hopkins, 1965). Average urinary and blood concentrations are 0.4 and 2.8 ug/100g, respectively (Casarett and Doull, 1979). Because of rapid clearance, blood concentration is not an indicator of Cr intake (Mertz, 1971).

D. Elimination

Chromium turnover in humans appears to be very slow (National Academy of Sciences, 1974). One component of chromium elimination has been calculated to have a half-life of 616 days (Taylor, 1975). In rats, three compartments for trivalent chromium have been estimated to have half-lives of 0.5, 5.9, and 83.4 days, respectively (Mertz, et al., 1965).

Chromium is excreted in both urine and feces. Urinary excretion is the major route of elimination, accounting for recovery of 80 percent of injected chromium (Mertz, 1969). Up to 20 percent of intravenously injected trivalent chromium was found in the feces of rats (Visek, et al. 1953). Milk

also contributes to excretion (Casarett, 1979).

IV. EFFECTS

A. Carcinogenicity

Carcinogenicity of various hexavalent Cr compounds in humans has been well documented (U.S. EPA, 1980). EPA's Carcinogen Assessment Group (CAG) has determined that there is substantial evidence that hexavalent Cr compounds are carcinogenic in man. Six epidemiologic studies, conducted at five different locations, of 1200 chromate workers provide strong evidence that inhalation of Cr VI produces lung cancer (U.S. EPA, 1978; 1980). One study (Taylor, 1966) also showed an increase in digestive cancer. In rats and hamsters inhalation studies using calcium chromates have produced cancer (Laskin, 1973), and Cr VI is carcinogenic when implanted in intrabronchial pellets, as well as by subcutaneous and intramuscular injection in mice and rats. However, the carcinogenicity of Cr VI has not been tested by oral administration (U.S. EPA, 1980).

The determination of the carcinogenicity of Cr VI compounds rests mainly on epidemiologic studies (see above) of employees in industries which use or produce chromates. Cr III compounds are used principally in the manufacture of ferrochrome, chromite bricks and steel, in leather tanning and in lithography. Data on the carcinogenicity of trivalent Cr are felt to be inadequate (Heimann, 1976). Rats showed a weak carcinogenic response to chromic (Cr III) acetate (Hueper and Payne, 1962;

Maltoni, 1974). Cr may be a co-carcinogen or promoter: chromium carbonyl is a mild synergist for benzo(a)pyrene in the production of carcinomas in tracheal grafts in rats (Lave and Mass, 1977). Such effects could be important in the development of lung cancer following pulmonary exposure to chromates.

B. Mutagenicity

Cytogenetic effects in workers exposed to welding fumes have been attributed to inhaled chromium (Hedenstedt, et al., 1977). These effects have also been reported in chromate production workers (Bigalief, et al., 1977).

Cr compounds induce chromosomal aberrations in human and animal leukocytes, and mutations in bacteria and yeasts (U.S. EPA, 1980; Petrilli and DeFlora, 1978a,b; Nakumoro 1978). In these tests Cr VI compounds have much higher activity than Cr III compounds. Under some assay conditions cellular reducing agents (ascorbic acid, NADH, NADPH, GSH) prevent Cr VI mutagenicity by reducing it to CR III (Petrilli and DeFlora, 1977; 1978a, b). Nakamuro, however (1978) found that Cr (III) acetate, nitrate and chloride induce chromosomal damage in cultured human leukocytes, and are bacterial mutagens.

C. Teratogenicity

Embryonic abnormalities have been produced in the developing chicken by direct injection of trivalent or hexavalent chromium into the yolk sac or onto the chorioallantoic membrane (Ridgway and Karnofsky, 1952). This effect

has not been further investigated, and is worrisome because of the reported placental permeability to complexed Cr (Mertz 1969).

D. Other Reproductive Effects

Pertinent information could not be located in the available literature.

E. Chronic Toxicity

Except as regards the carcinogenicity of Cr VI, the concentrations of Cr encountered in the normal environment do not constitute a human health hazard. However, acute and chronic toxicity problems associated with exposure to Cr are of concern in the industrial environment. These effects have been reviewed (NIOSH, 1975; EPA, 1980), and include damage to liver, kidney, skin, respiratory passages and lungs (U.S. EPA, 1978, 1980; NAS 1974, 1977; NIOSH, 1975). Allergic dermatitis is a pronounced property of both tri- and hexavalent Cr compounds (EPA, 1980; Casarett and Doull, 1979).

Subtle changes in pulmonary function have been observed in workers employed in electroplating (Bovett et. al., 1977). Cr VI causes ulceration and perforation of the nasal systems, chronic rhinitis and pharyngitis, but these effects have been observed only in workers chronically exposed to relatively high concentrations of chromates (NIOSH, 1975).

V. AQUATIC TOXICITY

A. Chronic Toxicity

No data for chronic toxicity of trivalent chromium

for freshwater fishes is available. The geometric mean of chronic toxicity values for the freshwater invertebrate Daphnia magna is based on data from a single study, and is reported as 445 ug/l. No chronic data for trivalent chromium for freshwater algae are available.

Chronic embryo-larval tests on six species of fresh water fish exposed to Cr VI resulted in values ranging from 37 to 72 ug/l for rainbow trout (Salmo gairdneri) and lake trout, Salvelinus mamaycush. White suckers, Catostomus commersoni, and channel catfish, Ictalurus punctatus, were intermediate in sensitivity and northern pike, Esox lucius, and bluegills, Lepomis macrochirus, were least sensitive with chronic values of 360 and 368 ug/l respectively. In life cycle or partial life cycle tests, both the rainbow trout and snook trout, Salvelinus fontinalis, were sensitive with chronic values of 265 ug/l. Chronic testing of hexavalent chromium in Daphnia magna found significant survival and fecundity changes at concentrations as low as 10 ug/l. The effects of hexavalent chromium on the freshwater algae, Chlamydomonas reinhardi, were recorded at levels as low as 10 ug/l. The Eurasian watermilfoil displayed the greatest resistance to hexavalent chromium, even at levels as high as 9,900 ug/l.

There are no chronic toxicity data available for trivalent chromium compounds in marine fish, invertebrates or algae.

The only available bioconcentration data for freshwater

species are from studies on rainbow trout, and indicate a bioconcentration factor of 1 for potassium chromate. Marine bioconcentration factors in three species of bivalve molluscs, Mytilus edulis, (34), Crassostrea Virginia (166), and Mya arenaria, (152), give a geometric mean of 114. The weighted average BEF is 11 (U.S. EPA, 1980).

B. Acute Toxicity

The acute toxicity of trivalent chromium compounds has been examined extensively. The 96-hour LC_{50} values for 14 tests ranged from 3,330 to 71,900 ug/l and correlates with the hardness of water over a range of 20 to 360 ug/l (as $CaCO_3$) in 11 species of freshwater fish. The guppy Poecilia reticulata was most sensitive and the bluegill the most resistant. Among eight species of freshwater invertebrates, acute 96-hour LC_{50} values ranged from 2,000 to 64,000 ug/l.

For hexavalent chromium 96-hour LC_{50} values ranged from 17,600 ug/l in the fathead minnow, Pimephales promelas, in soft water to 195,--- ug/l for large mouth bass, Micropteus salmoider, in hard water. The 96-hour LC_{50} values for freshwater invertebrates exposed to hexavalent chromium ranged from 3,100 ug/l in the rotifer, Philodina acuticornis, to 12,000 ug/l in the rotifer, Philodina roseola.

There are no pertinent acute toxicity data available regarding the toxicity of Cr III compounds to marine species.

The acute toxicity data for hexavalent chromium to marine fishes resulted in 96-hour LC_{50} values of 30,000 to 30,000

ug/l for the speckled sanddab, Citharichthys stigmaeus, and 91,000 ug/l for the mummichog, Fundulus heteroclitus. Invertebrates appeared more sensitive to hexavalent chromium than marine fish. The 96 hour LC_{50} values for hexavalent chromium ranged from 2,000 ug/l for the polychaete worm, Nereis vinens, to 105,000 ug/l for the mud snail, Nassarius obsoleutus, in static bioassays.

The U.S. EPA (1978) offers an extensive review of the environmental effects of chromium compounds in freshwater and marine organisms.

VI. EXISTING GUIDELINES

Standards promulgated by various U.S. agencies are summarized in Table I.

Based on animal data indicating carcinogenic effects of chromium VI and estimates of lifetime exposures from consumption of both drinking water and aquatic life forms, the U.S. EPA (1980) has estimated that the concentrations of hexavalent chromium in ambient water should be no greater than 7.1 ng/l to keep the lifetime risk of cancer below 1 in 100,000. This risk calculation is based on the conservative assumption that ingestion of Cr VI can cause cancer. EPA's Water Quality Criteria Document (U.S. EPA 1980) discusses this and alternative assumptions.

The OSHA time-weighted average exposure criterion for chromium (carcinogenic compounds) is 1 ug/m^3; for the "non-carcinogenic" classification of chromium compounds the criterion is 25 ug/m^3 (OSHA 1979).

TABLE 1

Recommended or Established Standards for Cr in the United States

MEDIUM	CHEMICAL SPECIES	REFERENCE	STANDARD
Drinking Water	Cr VI	U.S. Public Health Service (1962)	50 ug/l
Domestic Water Supply	total chromium	U.S. EPA (1976)	50 ug/l
Fresh Water (aquatic life)	total chromium	U.S. EPA (1976)	100 ug/l
Ambient Water Quality Criteria	total chromium[c]	U.S. EPA (1980)	50 ug/l
	Cr VI[c]	U.S. EPA (1980)	0.007 ug/l
Livestock Water	Cr VI	Nat'l. Acad. Sci. (1972) and Nat'l. Acad. Eng. (1972)	1 mg/l
Work Place AIR	carcinogenic Cr VI[a]	Nat'l. Inst. Occup. Safety and Health (1975)	1 ug/m^3
	noncarcinogenic Cr VI[a]	Nat'l. Inst. Occup. Safety and Health (1975)	25 ug/m^3 TWA[b] 50 ug/m^3 ceiling
	soluble chromic and chromous salts	29 CFR 1910.1000	0.5 mg/m^3
	metal and insoluble salts	29 CFR 1910.000	1.0 mg/m^3

[a]Carcinogenic compounds are here taken to include all forms of Cr VI other than CrO_3 and mono-or dichromates of H, Li, Na, K, Rb, Cs, and NH_4.

[b]Time-weighted average

[c]Corrected in 1980

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For the protection of aquatic species, proposed water criteria for both trivalent and hexavalent chromium in freshwater and marine environments have been prepared in accordance with the Guidelines for Deriving Water Quality Criteria (Federal Register 43:21506, May 18, 1975 and Federal Register 43:29028, July 5, 1978). In freshwater environments the proposed criterion for hexavalent chromium is 10 ug/l, not to exceed 110 ug/l, and the proposed criterion for trivalent Cr is given a Chronic Final Value represented by the following equation:

$$C.F.V. = e\ (0.83\ \ln(\text{water hardness}) = 2.94)$$

The proposed criterion for trivalent chromium in marine environments could not be determined by criteria established in the Guidelines.

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No. 52

Chrysene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated chrysene and has found sufficient evidence to indicate that this compound is carcinogenic.

CHRYSENE

Summary

Chrysene is a member of the polynuclear aromatic hydrocarbons (PAH) class. Numerous compounds in the PAH class are well-known as potent animal carcinogens. However, chrysene is generally regarded as only a weak carcinogen to animals. There are no reports available concerning the chronic toxicity of chrysene. Although exposure to chrysene in the environment occurs in conjunction with exposure to other PAH, it is not known how these compounds may interact in human systems.

No standard toxicity data for chrysene are available for freshwater or marine organisms.

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Polynuclear Aromatic Hydrocarbons (U.S. EPA, 1979a) and the Multi-media Health Assessment Document for Polycyclic Organic Matter (U.S. EPA, 1979b).

Chrysene ($C_{18}H_{12}$) is one of the family of polynuclear aromatic hydrocarbons (PAH) formed as a result of incomplete combustion of organic material. Its physical/chemical properties have not been well-characterized, other than a reported melting point of 254°C and a boiling point of 448°C (U.S. EPA, 1979b).

PAH, including chrysene, are ubiquitous in the environment, being found in ambient air, food, water, soils, and sediment (U.S. EPA, 1979b). The PAH class contains a number of potent carcinogens (e.g., benzo(a)pyrene), moderately active carcinogens (e.g., benzo(b)fluoranthene), weak carcinogens (e.g., chrysene), and cocarcinogens (e.g., fluoranthene), as well as numerous non-carcinogens (U.S. EPA, 1979b).

PAH which contain more than three rings (such as chrysene) are relatively stable in the environment and may be transported in air and water by adsorption to particulate matter. However, biodegradation and chemical treatment are effective in eliminating most PAH in the environment.

The reader is referred to the PAH Hazard Profile for more general discussion of PAH (U.S. EPA, 1979c).

II. EXPOSURE

A. Water

Levels of chrysene are not routinely monitored in water. However, the concentration of six representative PAH (benzo(a)pyrene, fluoranthene, benzo(k)fluoranthene, benzo(j)fluoranthene, benzo(g,h,i)perylene, and indeno(1,3-cd)pyrene) in U.S. drinking water averaged 13.5 ng/l (Basu and Saxena, 1977,1978).

B. Food

Chrysene has been detected in a wide variety of foods such as coconut oil (12 ppb), and smoked or cooked meats (up to 66 ppb) (U.S. EPA, 1979b). Although it is not possible to accurately estimate the human dietary intake of chrysene, it has been concluded (U.S. EPA, 1979b) that the daily dietary intake for all types of PAH is in the range of 1.6 to 16 ug. The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor for chrysene to be 3,100 for the edible portion of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficient for chrysene.

C. Inhalation

Chrysene is commonly found in ambient air. Measured concentrations of chrysene have reportedly been in the range of 0.6 to 4.8 ng/m^3 (Gordon, 1976; Fox and Staley, 1976). Thus, the human daily intake of chrysene by inhalation of ambient air may be in the range of 11.4 to 91.2 ng, assuming that a human breathes 19 m^3 of air per day.

III. PHARMACOKINETICS

Pertinent data could not be located in the available literature concerning the pharmacokinetics of chrysene or other PAH in humans. Nevertheless, it is possible to make limited assumptions based on the results of animal research conducted with several PAH, particularly benzo(a)pyrene.

A. Absorption

The absorption of chrysene in humans has not been studied. However, it is known (U.S. EPA, 1979a) that, as a class, PAH are well-absorbed across the respiratory and gastrointestinal epithelia. In particular, chrysene was reported to be readily transported across the gastrointestinal mucosa (Rees, et al. 1971). The high lipid solubility of compounds in the PAH class supports this observation.

B. Distribution

The distribution of chrysene in mammals has not been studied. However, it is known (U.S. EPA, 1979a) that other PAH are widely distributed throughout the body following their absorption in experimental rodents. Relative to other tissues, PAH tend to localize in body fat and fatty tissues (e.g., breast).

C. Metabolism

Limited work on the metabolism of chrysene has been conducted, as part of an investigation into the mechanism of its bioactivation to a mutagen/carcinogen (Wood, et al. 1977).

Chrysene, like other PAH, is apparently metabolized by the microsomal mixed-function oxidase enzyme system in mammals (U.S. EPA, 1979b). Metabolic attack on one or more of the aromatic double bonds leads to the formation of phenols, and isomeric dihydrodiols by the intermediate formation of reactive epoxides. Dihydrodiols are further metabolized by microsomal mixed-function oxidases to yield diol epoxides, compounds which are known to be biologically reactive intermediates for certain PAH. Removal of activated intermediates by conjugation with glutathione or glucuronic acid, or by further metabolism to tetrahydrotetrols, is a key step in protecting the organism from toxic interaction with cell macromolecules.

D. Excretion

The excretion of chrysene by mammals has not been studied. However, the excretion of closely related PAH is rapid, and occurs mainly via the feces (U.S. EPA, 1979a). Elimination in the bile may account for a significant percentage of administered PAH. However, the rate of disappearance of various PAH from the body, and the principal routes of excretion, are in-

fluenced both by the structure of the parent compound and the route of administration (U.S. EPA, 1979b). It is unlikely that PAH will accumulate in the body with chronic low-level exposures.

IV. EFFECTS

A. Carcinogenicity

Chrysene is regarded as a weak animal carcinogen (U.S. EPA, 1979b). LaVoie and coworkers (1979) reported that chrysene can act as both a tumor initiator and as a complete carcinogen on the skin of mice.

B. Mutagenicity

Chrysene is positive in the Ames Salmonella assay in the presence of a metabolizing enzyme system (LaVoie, et al. 1979; Wood, et al. 1977). Chrysene is also positive in the induction of sister-chromatid exchanges in Chinese hamster cells (Roszinsky-Kocher, et al. 1979).

C. Teratogenicity

Pertinent data could not be located in the available literature concerning the possible teratogenicity of chrysene. Other related PAH are apparently not significantly teratogenic in mammals (U.S. EPA, 1979a).

D. Other Reproductive Effects and Chronic Toxicity

Pertinent data could not be located in the available literature regarding other reproductive effects and chronic toxicity.

V. AQUATIC TOXICITY

The only data concerning the effects of chrysene to aquatic organisms is a single bioconcentration factor of 8.2 (24-hour) for the marine clam (Rangia cuneata) (Neff, et al. 1976). No standard aquatic toxicity data for chrysene either in acute or chronic studies are available for freshwater or marine species.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

There are no established exposure criteria for chrysene. However, PAH as a class are regulated by several authorities. The World Health Organization has recommended that the concentration of PAH in drinking water (measured as the total of fluoranthene, benzo(g,h,i)perylene, benzo(b)fluoranthene, benzo(h)fluoranthene, indeno(1,2,3-cd)pyrene, and benzo(a)pyrene) not exceed 0.2 µg/l. Occupational exposure criteria have been established for coke oven emissions, coal tar products, and coal tar pitch volatiles, all of which contain large amounts of PAH including chrysene (U.S. EPA, 1979a).

The U.S. EPA (1979a) draft recommended criteria for PAH in water are based upon the extrapolation of animal carcinogenicity data for benzo-(a)pyrene and dibenz(a,h)anthracene.

B. Aquatic

Data is insufficient for drafting freshwater or marine criterion.

CHRYSENE

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No. 53

Creosote

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated creosote and has found sufficient evidence to indicate that this compound is carcinogenic.

CREOSOTE

I. INTRODUCTION

Creosote is a coal-tar distillate used mainly as a wood preservative. It is highly toxic to wood-destroying organisms and has a low evaporation rate (Farm Chemicals Handbook, 1977). In 1972, an estimated 521,000 tonnes (575,000 tons) were produced by six companies at 25 sites in the United States (von Rumker, et al. 1974). About 90 percent of the creosote is sold to the wood-preservation industry; the remainder is burned as fuel (von Rumker, et al. 1974).

Creosote's other pesticidal uses are as an herbicide, an insecticide, an acaricide, an arachnicide, a fungicide, a tree dressing, a disinfectant, and a horse repellent (Table 1).

TABLE 1.

USES AND SITES FOR CREOSOTE
(Cummings, 1977)

Use	Site
Preservative	Wood
Insecticide (screwworm)	Horses and mules
Acaricide (mites)	Poultry and horses
Arachnicide (ticks)	Poultry and horses
Herbicide	Along roads, highways, and fences; farms; flower beds
Fungicide	Rope, canvas, tarpaulins, tree wounds
Insecticide (Certain insects, worms, moths and borers)	Tree dressing
Horse repellent	Wood stalls, mangers, gates, fence rails, posts, trees, trailer sites
Disinfectant	Outhouses, water closets, garbage cans, feeding and watering equipment

Creosote is produced by the distillation of coal tar obtained from the coking of coal. The composition of creosote is highly variable and depends on the composition of the coal used to make the tar, the design and operating conditions of the coke oven (e.g., gas collection system, temperature, coking time), and the design and operating condition of the still (e.g., feed rate, temperature, and blending of tar distillation fractions) (43 FR 48154, 1978).

Continuous tar distillation at temperatures of up to 400°C produces fractions typically ranging from crude benzene to residue pitches (von Rumker, et al. 1974). A common distillation temperature for creosote is about 200 to 400°C (Hawley, 1977; von Rumket, et al. 1974). The creosote fraction is a mixture of organic compounds, mainly liquid and solid cyclic hydrocarbons, including two-ring and polynuclear aromatic hydrocarbons (PAH) (Table 2). Among the PAH, phenanthrene represents 12 to 14 percent of the composition of creosote (Considine, 1976). Benzo(a)pyrene (BaP) is present at a concentration of about 200 ppm (Guerin, 1977).

II. EXPOSURE

A. Water

Each year an estimated 60 to 115 million pounds (27,000-52,000 tonnes) of creosote are discharged in wastewater treatment sludges by creosote producers. At large tar distillation plants, wastewater streams containing creosote are treated on-site and/or conveyed to public sewage treatment facilities. Wastewater sludges treated on-site are transferred to landfill or burial sites (von Rumker, et al. 1974). The estimated flux of creosote from these disposal sites ranges from 0.75 $kg/m^2/hr$ to 11.0 $kg/m^2/yr$ (U.S. EPA, 1980). In 1972, about one billion pounds (455,000

TABLE 2.

PHYSICAL AND CHEMICAL PROPERTIES OF CREOSOTE

Synonyms: Brick oil, coal tar oil, creosote oil, creosotum, cresylic creosote, dead oil, heavy oil, liquid pitch oil, naphthalene oil, tar oil, wash oil

Structural and Empirical Formula: Consists principally of liquid and solid cyclic hydrocarbons; contains substantial amounts of naphthalene and anthracene; 12-14 percent phenanthrene; 200 ppm benz(a)pyrene

Molecular Weight: ---

Description: Dark brown green, yellowish or colorless above 38°C, naphthenic odor; soluble in alcohol, benzene toluene; immiscible with water

Specific Gravity and/or Density: d^{25}_{25} more than 1.076

Melting and/or Boiling Points: Common distillation range 200 to 400°C

Stability: Overall degradation rate (0.48/day) = same as microbial degradation

Solubility (water): approx. 5 g/l; $\frac{sed}{H_2O} \cdot \frac{.2}{1}$

Vapor Pressure: ---

Bioconcentration Factor (BCF) and/or
Octanol/water partition coefficient (K_{ow}): BCF = 0.6
K_{ow} = 1.0

Source: Hawley, G.G., 1977; Windholz, 1976; U.S. EPA, 1980; Lopedes, 1978

tonnes) of creosote were used to preserve railroad ties, marine pilings and utility poles (NIOSH, 1977a).

Some of the organics present in creosote are moderately soluble. Creosote partitions between sediments and water in a ratio of 1:5. It is considered stable in groundwater, but decomposes at an estimated rate of 90 percent in five days in river water flowing 50-250 miles. About 99 percent decomposed in a lake environment in one year (U.S. EPA, 1980).

Creosote migrates from treated wood into the environment, but the impact of this migration is unknown. Creosote was found to have a vapor loss of 27.5 and 15.2 percent from the outer two inches of seasoned and green poles, respectively; high residue creosote was estimated to have a 10.3 and 4.4 vapor loss, respectively. Creosote losses to the aquatic environment are the greatest during the first years after installation. One eight-year study is summarized below (43 FR 48154, 1978).

Year	Creosote Loss pounds/linear foot
1	0.31
2	0.05
3	0.06
4	0.22
4-8	0.15 (average)

B. Food

Naiussat and Auger (1970) found that PAHs in a contaminated lagoon accumulated to the greatest extent in species near the top of the food chain. One of these compounds, BaP, has been reported to accumulate in mussels (about 50 µg/kg; 20 times background) taken from creosote-treated pilings (43 FR 48154, 1978). Elevated levels of BaP in mussels growing near creosoted timbers or pilings suggest that creosote is a significant source of BaP in the marine environment. This suggestion was supported by compari-

sons of gas chromatography profiles of polycyclic aromatic hydrocarbons isolated from mussels and creosoted wood (Dunn and Stich, 1976).

High levels of PAH have been found in commercial seafoods grown in impoundments constructed of creosoted wood. Commercial samples of oysters, clams, and mussels were found to contain BaP at concentrations generally less than 10 ng/g (wet weight). PAHs were also found in cockels, abalone, scallops, lobster, and shrimp. Levels of BaP and other related PAHs were found to be inversely related to the ability of the species to metabolize PAH, except in the case of lobster. Unexpectedly high levels were found in all edible meat of lobsters maintained in commercial tidal compounds constructed of creosoted timber: up to 281 ng/g BaP, 303 ng/g chrysene, 222 ng/g benzo(a)anthracene, 261 ng/g benzo(b)fluoranthene, 153 ng/g dibenz-(a,h)anthracene, and 137 ng/g indeno(1,2,3-cd)pyrene (Dunn and Fee, 1979).

III. PHARMACOKINETICS

A. Absorption

Creosote is (readily) absorbed through the skin and mucous membranes (NIOSH, 1977b).

IV. EFFECTS

A. Carcinogenicity

Creosote has been associated with several occupational cases of skin cancer over a 50-year period (Farm Chemicals Handbook, 1977); its role in human cancer is still not clearly understood (NIOSH, 1977b).

Henry (1947), Lenson (1956), O'Donovan (1920), Cookson (1924), and Mackenzie (1898) described various kinds of workers who were occupationally exposed to creosote and developed skin tumors. Dermal application of creosote produced skin tumors in mice (Woodhouse, 1950; Poel and Kammer, 1957; Lijinsky, et al. 1956; Boutwell and Bosch, 1958; Roe, et al. 1958). Roe, et

al. (1958) also found that dermal application of creosote to mice produced lung tumors. Boutwell and Bosch (1958) found that creosote had the ability to initiate tumor formation when applied for a limited period prior to treatment with croton oil. Sall and Shear (1940) found that the number of skin tumors was increased by dermal treatment with creosote and benzo(a)pyrene over the number of tumors produced by benzo(a)pyrene or creosote alone. There is considerable evidence to show that creosote produces tumors in mice; that creosote, when applied dermally, is a tumor-initiating agent when followed by dermal treatment with croton oil (Boutwell and Bosch, 1958); that creosote accelerates the tumor production caused by benzo(a)pyrene (Sall and Shear, 1940); and that workers occupationally exposed to creosote developed tumors (Table 3). These studies have not yet demonstrated a correlation between the carcinogenic potency of creosote oils and the content of benzpyrene (Patty, 1963).

Results from dose response studies are summarized below (NIOSH, 1977a).

Concentration and duration	Effects
100% 3x/wk 28 wk	Skin carcinomas in 82%, tumors in 92%
20-80% 3x/wk 6-44 wk	Skin carcinomas in 88%, tumors in 100%
100% 2x/wk 21 wk	Skin and lung tumors in 74%
100% 3x/wk 70 wk	Skin tumors in 50%
10-100% 2x/wk* 70 wk	Skin tumors in 38-74%
2% 2x/wk* 70 wk	No tumors

*Creosote plus 1 percent 7,12-dimethylbenz(a)anthracene.

TABLE 3.

SUMMARY TABLE ON ONCOGENICITY OF CREOSOTE

A. Human Case Reports

Authors	Year	Substance and Type of Exposure	Occupation of Exposed Individual(s)	Type of Tumor Response
Mackenzie	1896	Handling of Creosote	Worker who dipped railway ties in creosote	Warty elevation on arms; papillomatous swellings on scrotum
O'Donovan	1920	Handling of Creosote	Workers who creosoted timbers	Skin cancer
Cookson	1924	Handling of Creosote	Creosote factory worker	Squamous epitheliomata on hand; epitheliomatous deposits in liver, lungs, kidneys and heart walls
Henry	1947	Handling of Creosote	37 men of various occupations	Cutaneous epitheliomata
Lenson	1956	Painting of Creosote	Shipyard worker	Malignant cutaneous tumors of the face

B. Animal Studies

Dermal Exposure

Authors	Year	Substance Tested	Animal and Strain	Type of Tumor Response
Sall and Shear	1940	Creosote and benzo(a)pyrene	Mice (Strain A)	Accelerated tumor formation
Woodhouse	1950	Creosote oil	Mice (Albino; Undefined strain)	Papillomas and carcinomas
Lijinsky, et al.	1956	#1 creosote oil	Mice - Swiss	Papillomas and carcinomas
Poel and Kammer	1957	Blended creosote oils;	Mice (C57L Strain)	Papillomas and carcinomas metastatic growths in lungs and lymph nodes
		Light creosote oil	Mice (C57L Strain)	Papillomas
Boutwell and Bosch	1958	Creosote (Carbasota)	Mice (Albino - random bred)	Papillomas and carcinomas
Roe, et al.	1958	Creosote oil (Carbasota)	Mice (Strain Undefined)	Skin and lung tumors

B. Mutagenicity

Simmon and Poole (1978) found that, following metabolic activation by Arochlor 1254-stimulated rat liver homogenate, both the creosote P1 and the coal tar-creosote P2 produced a mutagenic dose-response and a doubling above background mutation rate with Salmonella typhimurium strains TA 1537, TA 98, and TA 100. Mitchell and Tajiri (1978) found that, following metabolic activation by Arochlor 1254-stimulated rat liver homogenate, creosote P1 and coal tar creosote P2 increased the number of forward mutations at the thymidine kinase locus of L5178Y mouse lymphoma cells in a dose-related manner. There is considerable evidence which proves that creosote P1 and P2 cause mutations in Salmonella typhimurium strains TA 1537, TA 98 and TA 100, and in L5178Y mouse lymphoma cells.

C. Teratogenicity and Other Reproductive Effects

Investigations utilizing pregnant swine indicate that direct contact with lumber freshly treated with creosote would produce acute toxicosis, resulting in extensive mortality in newborn swine. The direct contact of the pregnant sow with lumber freshly treated with creosote provides sufficient dermal absorption to cause fetal deaths and weak pigs at birth. Creosote is extremely toxic to young swine; the degree of toxicity lessens as the pigs become older (Schipper, 1961).

D. Chronic and Acute Toxicity

Skin contact with creosote or exposure to its vapors may cuase burning, itching, papular and vasicular eruptions, or gangrene. Eye injuries can include keratitis, conjunctivitis, and corneal abrasion (Patty, 1963). Exposed skin shows increased susceptibility to sunburn, an effect attributed to photo-toxic substances usually present in commercial grades of creosote. Eventually, exposed skin areas become hyperpigmented (NIOSH, 1977b).

Serious systemic effects, including cardiovascular collapse and death, have been observed only after ingestion (NIOSH, 1977b). Fatalities have occurred within 14 to 36 hours after ingestion of 7 grams by adults or 1 to 2 grams by children. Symptoms of systemic illness include salivation, vomiting, respiratory difficulties, vertigo, hypothermia, cyanosis, and mild convulsion (Patty, 1963). Once widely used in medicine, occasional instances of self-medication are still reported and sometimes lead to chronic visual disturbances, hypertension, and gastrointestinal bleeding (NIOSH, 1977b).

The oral LD_{50} in rats is estimated at 725 mg creosote per kilogram body weight (mg/kg). The reported LD_{Lo} for dogs, cats, and rabbits is 600 mg/kg (Fairchild, 1977).

V. AQUATIC TOXICITY

Ellis (1943) found fish kills occurring at creosote concentrations as low as 6.0 mg/l in less than 10 hours. Applegate, et al. (1957), using small numbers of subjects, found that concentrations of 5.0 mg/l produced no mortalities in rainbow trout (Salmo gainneri), bluegill (Lepomis macrochirus), or lamprey larvae (Petromyzon marinus).

The 8-day LD_{50} of a 60:40 mixture of creosote and coal tar in bobwhite quail (Colinus virginianus) was reported to be about 1,260 ppm; in the mallard duck (Anas platyrhynchos), 10,388 ppm. The 24-hour 50 percent medium tolerance limit (TL_{50}) of the creosote/coal tar mixture was 3.72 ppm in rainbow trout (Salmo gainneri) and 4.42 ppm in the bluegill (Lepomis macrochirus). The 24-hour TL_{50} concentrations in goldfish (Carrasius auratus) and rainbow trout were 3.51 and 2.6 ppm, respectively (Webb, 1975).

VI. EXISTING GUIDELINES AND STANDARDS

The Office of Toxic Substances of EPA has issued RPAR on creosote and is continuing preregulatory assessment under Section 6 of the Federal Insecticide, Fungicide and Rodenticide Act.

A time-weighted average creosote concentration of 0.1 mg/m^3 has been recommended for occupational air exposure.

The aquatic toxicity rating for creosote is reported as TLm_{96} = 10-1 ppm (Fairchild, 1977).

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No. 54

Cresols and Cresylic Acid

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

Cresol and Cresylic Acid

I. INTRODUCTION

Cresols are methyl phenols with methyl group at the o-, p-, m- position. It has a molecular weight of 108, a melting point of between 11-35°C and a boiling point of between 191-203°C. It is slightly soluble in water, but soluble in alcohols, glycols, dilute alkalis, ether and chloroform. Cresylic acid is the refined product from coal tar and contains the three isomers of cresol (the crude product from coal tar is creosote).

Cresols are quite stable in soil due to their antimicrobial properties. o-cresol is degraded in air to quinones and dihydroxybenzene by O_3 with an estimated half-life of 1 day. The m- and p- isomers are expected to behave similarly.

Cresols are used as disinfectants, agricultural chemicals, solvents, chemical intermediates, metal cleaners, and motor oil additives. p-cresol is permitted in U.S. as a food flavoring and for fragrance in soaps, lotions and perfumes. Annual production if 150 million pounds. NIOSH[1] estimates that the annual environmental release of the mixed isomers is 30 million pounds.

II. PHARMACOKINETICS

Cresols are rapidly metabolized and thus unlikely to bioaccumulate in mammals.[2]

III. EFFECTS ON MAMMALS

A. Carcinogenicity: CAG[2] concluded that the data base

for this chemical is weak. No data exist on which to determine carcinogenesis in mice. The literature cites three case reports of cancer in humans occupationaly exposed.

B. Mutagenicity: CAG[2] concluded that cresols cause chromosome fragmentation in plants. No other mutagenicity studies have been done.[2]

C. Toxicity: They are corrosive to the skin and mucuous membranes and moderately toxic by ingestion and dermal exposure. The organs affected are CNS, liver, lung, kidneys, stomach, eyes, and heart. No epidemiological studies of workers have been done.[1]

IV. EXISTING GUIDELINES

The current occupational standard (TWA) is 5 ppm. NIOSH[1] recommends a lowering to 2.3 ppm.

DOSSIER

ON

CRESOLS

BY

Clement Associates, Inc.
1055 Thomas Jefferson Street, NW
Washington, D.C. 20007

December, 1977

Contract No. NSF-C-ENV77-15417

Prepared for

TSCA Interagency Testing Committee
Washington, D.C.

54-5

FOREWORD

This dossier has been prepared by Clement Associates, Inc. (Clement), in partial fulfillment of Contract NSF-C-ENV77-15417, sponsored by the National Science Foundation, to provide technical support to the Toxic Substances Control Act (TSCA) Interagency Testing Committee. The Committee is charged with the responsibility for making recommendations to the Administrator of the Environmental Protection Agency (EPA) regarding chemical substances or mixtures which should be given priority by EPA for testing to determine adverse effects on man or the environment.

The dossier was designed to provide the Committee with information on the chemical's physical and chemical properties, exposure characteristics, and biological properties in sufficient detail to support an informed judgment on whether the substance should be given priority for testing. The dossier is not intended to represent a comprehensive critical review. Such a review could not be performed with the constraints imposed upon the Committee (and, therefore, the contractor) by the statutory deadlines of TSCA.

Faced with the task of preparing dossiers which could be quickly assembled and yet contain sufficient information for the Committee's purposes, Clement proceeded along the following lines.

Literature searches were conducted using the National Library of Medicine's TOXLINE and the Environmental Mutagen Information Center (EMIC) automated data banks. Each reference on a list of sources of general information (see "General References" in bibliography) was reviewed. Further references and information were obtained from monographs, criteria documents, reviews, and reports available from government agency files and trade association libraries. Information received in response to the Committee's July 1977 Federal Register notice requesting information on certain substances was reviewed. Clement scientists relied upon their own knowledge of the literature to augment the data sources.

In general, secondary sources were relied upon in preparing the dossiers. When an article was judged to contain information of major significance or to require a critical review the primary source was consulted. The text makes clear whether a primary or secondary source of information was used.

KEY TO ABBREVIATIONS

TCLo - Lowest published toxic concentration
- the concentration of a substance in air which has been reported to produce any toxic effect in animals or humans over any given exposure time.

TDLo - Lowest published toxic dose
- the lowest dose of a substance introduced by any route other than inhalation over any given period of time that has been reported to produce any toxic effect in animals or humans.

LCLo - Lowest published lethal concentration
- the lowest concentration of a substance, other than an LC50, in air that has been reported to have caused death in humans or animals over any given exposure time.

LDLo - Lowest published lethal dose
- the lowest dose of a substance other than LD50 introduced by any route other than inhalation over any given period of time that has been reported to have caused death in humans or animals.

LC50 - Median lethal concentration
- the concentration of a test material that kills 50 per cent of an experimental animal population within a given time period.

LD50 - Median lethal dose
- the dose of a test material, introduced by any route other than inhalation, that kills 50 percent of an experimental animal population within a given time period.

LT50 - Median Lethal Response Time
-Statistical estimate of the time from dosage to the death of 50 percent of the organisms in the population subjected to a toxicant under specified conditions.

TLm - Median tolerance limit
- the concentration of a test material at which 50 per cent of an experimental animal population are able to survive for a specified time period.

TLV® - Threshold limit value
- the airborne concentration of a substance to which nearly all workers may be repeatedly exposed day after day without adverse effect.

TLV®-TWA - Threshold limit value - time weighted average
- the time-weighted average concentration of a substance for an 8-hour workday or 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

TLV®-STEL- Threshold limit value - short term exposure limit-
- the maximal concentration of a substance to which workers can be exposed for up to 15 minutes without suffering acute or chronic toxic effects. No more than four excursions per day are permitted. There must be at least 60 minutes between exposure periods. The daily TLV-TWA must not be exceeded.

BOD - Biochemical oxygen demand
- a measure of the presence of organic materials which will be oxidized biologically in bodies of water.

NOHS Occupational Exposure:

- Rank
  - an ordering of the approximately 7000 hazards occurring in the workplace from most common to least common

- Estimated number of persons exposed
  - includes full- and part-time workers. For hazards ranked 1 through 200, the figure projected to national statistics by NIOSH is given; for the remaining hazards the number of people exposed given in the survey was multiplied by a fixed number to give a rough estimate of national exposure. The fixed number used, --30--, is derived from the statistical sampling technique used in this survey.

i - insoluble

ss - slightly soluble

s - soluble

vs - very soluble

∞ - soluble in all proportions

bz - benzene

chl - chloroform

eth	- ether
peth	- petroleum ether
ace	- acetone
lig	- ligroin
alc	- alcohol
CCl_4	- carbon tetrachloride
dil. alk.	- dilute alkalis
CS_2	- carbon disulfide
os	- organic solvents
oos	- ordinary organic solvents

CRESOLS

AN OVERVIEW

There are three isomers of cresol: o-cresol, m-cresol, and p-cresol. All three isomers as well as mixtures are articles of commerce. Cresols are solid or liquid at room temperature (melting points 11-35°C). They are slightly soluble in water and soluble in organic solvents.

Total annual production of cresols in the United States is probably in excess of 100 million pounds. They are used for a wide variety of purposes, including uses as disinfectants, solvents, in ore flotation, and as intermediates in the production of phosphate esters and phenolic resins. The number of persons occupationally exposed to cresols is estimated to be two million. They are also present in a number of consumer procucts, including disinfectants, metal cleaners, and motor oil additives.

Cresols are manufactured both from petroleum and from coal. The composition of the commercial products depends on the method of production and upon the degree of refining. Cresols are sold in a wide variety of grades, varying in composition, color, and boiling range. Technical grade cresols commonly contain xylenols and phenol. A less refined product called creosote oil contains 10-20% by volume of tar from the coking process.

Cresols are relatively easily metabolized by mammals and micro-organisms and are unlikely to undergo significant bio-accumulation. They are moderately toxic to mammals by ingestion and dermal exposure, and are corrosive to skin and other tissues. No data are available on their toxicity by inhalation. Little information is available on effects of chronic exposure.

In one experiment all three isomers of cresol were reported to promote the carcinogenicity of dimethylbenzanthracene on mouse skin. m-Cresol caused developmental abnormalities in toad embryos. Otherwise, no significant information is available on the potential carcinogenicity, mutagenicity, or teratogenicity of cresols.

Cresols have a broad spectrum of toxicity to micro-organisms and are used as disinfectants and fungicides. There is little other information on their potential toxicity to wildlife.

CRESOLS

PART I

GENERAL INFORMATION

I. Cresol (mixed isomers)

1.1 Identification

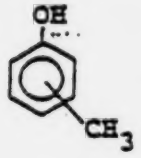
CAS No. 001319773
NIOSH No. GO59500

1.2 Synonyms and Trade Names

Cresylic acid; methyl phenol; hydroxytoluene; tricresol; cresylol

(G23,G21,G16)

1.3 Chemical Formula and Molecular Weight



C_7H_8O Mol. Wt. 108.15

(G23)

1.4 Chemical and Physical Properties

1.4.1 Description: A mixture of isomers in which m-isomer predominates, obtained from coal tar or petroleum; colorless, yellow or pinkish liquid; phenolic odor; combustible; becomes darker with age and on exposure to light.

(G21,G23)

1.4.2 Boiling Point: 191 - 203° C (G21)

1.4.3 Melting Point: 11 - 35° C (G21)

1.4.4 Absorption Spectrometry:

No information found in sources searched

1.4.5 Vapor Pressure: No information found in sources searched

1.4.6 Solubility: Soluble in alcohol, glycol, dilute alkalis, ether, chloroform; Slightly soluble in water

(G21,G25)

1.4.7 Octanol/Water Partition Coefficient:

Log P_{oct} = 2.70 (estimate)

1.5 Production and Use

1.5.1 Production: ~60 Million lbs (1968)
~80 Million lbs (1973)
(G25)

1.5.2 Use: As a disinfectant; intermediate in manufacturing of phenolic resins, tricresyl phosphate, salicylaldehyde, coumarin, and herbicides; as an ore flotation agent; as a textile scouring agent; as an organic intermediate; as a surfactant
(G21)

Quantitative Distribution of Uses:

	Percent
Phosphate esters	22
Magnet wire	15
Antioxidants	15
Resins	15
Exports	10
Cleaning and disinfectant compounds	6
Ore flotation	6
Miscellaneous	11
	100 (G25)

Consumer Product Information:

Cresol is present in:

automotive parts cleaner
metal cleaner, stripper, degreaser
disinfectant
motor oil additive
carbon remover
embalming supplies
(G35)

1.6 Exposure Estimates

1.6.1 Release Rate: 30.4 Million lbs, (G28)

1.6.2 NOHS Occupational Exposure:

Rank: 105

Estimates no. of persons exposed: 1,914,000
(G29)

II. m-Cresol

1.1 Identification

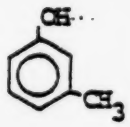
CAS No.: 000108394
NIOSH No.: GO61250

1.2 Synonyms and Trade Names

m-Cresylic acid; m-methylphenol; 3-methylphenol; 1-hydroxy-3-methylbenzene; m-kresol; m-oxytoluene

(G16)

1.3 Chemical Formula and Molecular Weight



C_7H_8O Mol. wt. 108.15

(G22)

1.4 Chemical and Physical Properties

1.4.1 Description: Colorless to yellowish liquid; phenol-like odor (G21)

1.4.2 Boiling Point: 202.2° C (G22)

1.4.3 Melting Point: 11.5° C (G22)

1.4.4 Absorption Spectrometry:

λ_{max}^{hexane} = 214, 271, 277

log ϵ = 3.79, 3.20, 3.27 (G22)

1.4.5 Vapor Pressure: 1 mm at 52.0° C (G22)

1.4.6 Solubility: Slightly soluble in water; Soluble in hot water, organic solvents; Soluble in all proportions in alcohol, ether, acetone, benzene and carbon tetrachloride

(G22)

1.4.7 Octanol/Water Partition Coefficient:

$\log P_{oct} = 2.37$ (G15)

1.5 Production and Use

1.5.1 Production:

No information found in sources searched

1.5.2 Use:

In disinfectants and fumigants; in photographic developers, explosives (G23)

1.6 Exposure Estimates

1.6.1 Release Rate:

No information found in sources searched

1.6.2 NCHS Occupational Exposure:

Rank: 2781

Estimated no. of persons exposed: 9,000*

*rough estimate (G29)

1.7 Manufacturers

Koppers Co., Inc. (G24)

III. o-Cresol

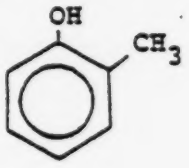
1.1 Identification — CAS No. 000095487
NIOSH No. GO63000

1.2 Synonyms and Trade Names

o-Cresylic acid; o-methyl phenol; 2-methyl phenol; orthocresol; 1-hydroxy-2-methylbenzene; o-hydroxytoluene; o-methylphenol; o-oxytoluene; 2-hydroxytoluene

(G16)

1.3 Chemical Formula and Molecular Weight



C_7H_8O Mol. Wt. 108.15

(G22)

1.4 Chemical and Physical Properties

1.4.1 Description: White crystals; phenol-like odor; combustible; becomes dark with age and exposure to air and light. (G23,G21)

1.4.2 Boiling Point: 190.95° C (G22)

1.4.3 Melting Point: 30.94° C (G22)

1.4.4 Absorption Spectrometry:

λ^{Water}_{Max} = 219, 275 nm,

log ε = 3.71, 3.22 (G22)

1.4.5 Vapor Pressure: 1 mm at 38.2° C (G22)

1.4.6 Solubility: Soluble in water and ordinary organic solvents;
Very soluble in alcohol and ether;
Soluble in all proportions in acetone, benzene, carbon tetrachloride

(G22)

1.4.7 Octanol/Water Partition Coefficient:

$$\text{Log } P_{oct} = 3.40 \qquad \text{(G15)}$$

1.5 Production and Use

1.5.1 Production:

49.700	Million lbs	(1972)	(G28)
20.481	Million lbs	(1975)	(G24)
22.187	Million lbs	(1976)	(G24)

1.5.2 Use: Disinfectant; solvent (G23)

1.6 Exposure Estimates

1.6.1 Release Rate: 15.6 Million lbs (G28)

1.6.2 NOHS Occupational Exposure:

Rank: 1480

Estimates no. of persons exposed: 52,000*

*rough estimate (G29)

1.7 Manufacturers

from coal tar:

Koppers Co., Inc.
Ferro Corp.

from petroleum:

Merichem Co.
Ferro Corp.
Sherwin-Williams Co.

(G24)

CRESOLS

IV. p-Cresol

1.1 Identification CAS No.: 000106445
NIOSH No.: GO64750

1.2 Synonyms and Trade Names

4-Cresol; p-cresylic acid; 1-hydroxy-4-methylbenzene; p-hydroxytoluene; 4-hydroxytoluene; p-kresol; 1-methyl-4-hydroxybenzene; p-methylphenol; 4-methylphenol; p-oxytoluene; para-cresol; paramethyl phenol (G16)

1.3 Chemical Formula and Molecular Weight

C_7H_8O Mol. wt. 108.15 (G22)

1.4 Chemical and Physical Properties

1.4.1 Description: Crystalline mass; phenol-like odor (G21)

1.4.2 Boiling Point: 201.9° C (G22)

1.4.3 Melting Point: 34.8° C (G22)

1.4.4 Absorption Spectrometry:

$\lambda_{max}^{cyclohexane}$ = 280 nm

log ϵ = 3.23 (G22)

1.4.5 Vapor Pressure: 1 mm at 53.0° C (G22)

1.4.6 Solubility: Slightly soluble in water; Soluble in hot water, organic solvents; Soluble in all proportions in alcohol, ether, acetone, benzene and carbon tetrachloride (G22)

1.4.7 Octanol/Water Partition Coefficient

Log P_{oct} = 2.35 (G15)

1.5 Production and Use

1.5.1 Production:

No information found in sources searched

1.5.2 Use:

As a chemical intermediate (G24)

1.6 Exposure Estimate

1.6.1 Release Rate:

No information found in sources searched

1.6.2 NOHS Occupational Exposure

Rank: 2466

Estimated no. of persons exposed: 14,000*

*rough estimate

(G29)

1.7 Manufacturers

Sherwin-Williams Co.

(G24)

CRESOLS

SUMMARY OF CHARACTERISTICS

Name	Solubility	Log P_{oct}	Estimated Environmental Release (Million lbs)	Production (Million lbs)	Estimated no. of persons exposed (occupational)	Use
Cresol (mixed isomers)	s in alc, glycol, dil. alk, eth, chl. ss in H_2O	2.70	30.4	~60 (1968) ~80 (1973)	1,914,000	Disinfectant; phenolic resins; tricresyl phosphate; ore flotation; textile scouring agent; organic intermediate; mfg. of salicylaldehyde coumarin, and herbicides surfactant
o-Cresol	s in H_2O and OOS. vs in alc and eth. oo in ace, bz, CCl_4.	1.40	15.6	49.7 (1972) 20.481(1975) 22.187(1976)	~ 52,000	Disinfectant, solvent
m-Cresol	ss in H_2O; s in hot H_2O, os; oo in alc, eth, bz, ace, CCl_4	2.37	*	*	~ 9,000	In disinfectants, fumigants, photographic developers, explosives
p-Cresol	ss in H_2O; s in hot H_2O, os; oo in alc, eth, bz, ace, CCl_4	2.35	*	*	~ 14,000	cyclic intermediate

* No information found in sources searched.

CRESOLS

PART II

BIOLOGICAL PROPERTIES

2.1 Bioaccumulation

Log octanol/water partition coefficients are 3.40, 2.37, and 2.35 for the o-, m-, and p-isomers, respectively (G15). The high partition coefficient of the o-isomer is due to the steric effect of the methyl group on the hydroxyl group. The high octanol/water partition coefficients of the cresols indicate that bioaccumulation in aquatic organisms is a possibility, but specific data on such bioaccumulation are not available. By analogy with phenol, which appears to be completely eliminated from the body within 24 hours (G19), it is expected that cresols would not be bioaccumulated in mammals. Cresols in waste waters near industrial plants are reported to undergo rapid biodegradation (G14), which indicates that cresols, like phenol, are relatively easily metabolized.

2.2 Contaminants and Environmental Degradation or Conversion Products

Cresols are sold in a wide variety of technical and special grades, classified by color and distillation range (G25). The composition of the various materials depends upon the starting material and the method of production. A major source of cresols is the tar-acid oil obtained as a by-product of coking of coal (G25).

Cresols (boiling above 204°C), available as a mixture of o-, m-, and p-isomers from tar acids are called cresylic acid. A less refined product called creosote oil contains 10-20% by volume of the tar from the coking process; it is used as a wood preservative (G25). Creosote oil may contain polynuclear aromatic hydrocarbons. Xylenols and phenol are common impurities (or ingredients) of technical grade cresols (G25).

The high environmental stability of the cresols in soils (owing to their antimicrobial properties) contributes to their widespread use as wood perservatives. o-Cresol is degraded by the hydroxyl radical and ozone in air and by organic peroxide radicals in water; half life estimates are less than 1 day in air and 10 days in water (G14). The m- and p-isomers are expected to behave similarly. Environmental degradation is likely to be by air oxidation to give quinones and dihydroxybenzenes (G14).

Biodegradation products of cresols by sewage microorganisms include carbon dioxide, methane, 3-methylcatechol, 2-hydroxy-6-oxahepta-2,4-dienoic acid, oxalic acid, pyrocatechol, carboxylic acid, and salicylic acid (G14). By analogy with phenol, cresols may be methylated in the environment to form the corresponding anisoles.

2.3 Acute Toxicity

The NIOSH Registry of Toxic Effects of Chemical Substances (G16) reports the acute toxicity of cresols as follows:

Substance	Parameter	Dosage	Animal	Route
Cresol	LD50	1454 mg/kg	rat	oral
	LD50	861 mg/kg	mouse	oral
o-Cresol	LD50	121 mg/kg	rat	oral
	LD50	1100 mg/kg	rat	skin
	LD50	344 mg/kg	mouse	oral
	LDLo	410 mg/kg	mouse	subcutaneous
	LDLo	55 mg/kg	cat	subcutaneous
	LDLo	940 mg/kg	rabbit	oral
	LD50	1380 mg/kg	rabbit	skin
	LDLo	450 mg/kg	rabbit	subcutaneous
	LDLo	180 mg/kg	rabbit	intravenous
	LDLo	360 mg/kg	guinea pig	intraperitoneal
	LDLo	200 mg/kg	frog	subcutaneous
m-Cresol	LD50	242 mg/kg	rat	oral
	LD50	620 mg/kg	rat	skin
	LD50	350 mg/kg	rat	unknown
	LD50	828 mg/kg	mouse	oral
	LDLo	450 mg/kg	mouse	subcutaneous
	LDLo	180 mg/kg	cat	subcutaneous
	LDLo	1400 mg/kg	rabbit	oral
	LD50	2050 mg/kg	rabbit	skin
	LDLo	500 mg/kg	rabbit	subcutaneous
	LDLo	280 mg/kg	rabbit	intravenous
	LDLo	100 mg/kg	guinea pig	intraperitoneal
	LDLo	250 mg/kg	frog	subcutaneous

(continued)

Substance	Parameter	Dosage	Animal	Route
p-Cresol	LD50	207 mg/kg	rat	oral
	LD50	705 mg/kg	rat	skin
	LD50	344 mg/kg	mouse	oral
	LDLo	150 mg/kg	mouse	subcutaneous
	LD50	160 mg/kg	mouse	unknown
	LDLo	80 mg/kg	cat	subcutaneous
	LDLo	620 mg/kg	rabbit	oral
	LD50	301 mg/kg	rabbit	skin
	LDLo	300 mg/kg	rabbit	subcutaneous
	LDLo	180 mg/kg	rabbit	intravenous
	LDLo	100 mg/kg	guinea pig	intraperitoneal
	LDLo	150 mg/kg	frog	subcutaneous

Cresols are rated as moderately toxic to humans (G4). Acute exposures can cause muscular weakness, gastroenteric disturbances, severe depression, collapse, and death (G38). Organs attacked by cresols include the central nervous system, liver, kidneys, lungs, pancreas, spleen, eyes, heart, and skin (G38). The type of exposure to cresols determines, in part, the toxic effects. Cresols are highly corrosive to any tissues they contact (G5) and are readily absorbed by skin and mucous membranes. Systemic effects, including death, occur after dermal exposure. Because their vapor pressure is low at 25°C, cresols do not usually constitute an acute inhalation hazard. No data are available on the toxicity of cresol vapors to humans (G39).

In animals, cresol toxicity varies with the isomer, the species and the route of exposure. Reported LD50s vary from a low of 121 mg/kg in the rat (oral, o-cresol) to a high of 2050 mg/kg in the rabbit (skin, m-cresol) (G16). Evidence for different biological effects of the three isomers includes the observation that the ratios between the LD50s of the least toxic and most toxic isomers vary from as low as 1.8 (cutaneous, rat) to as high as 6.8 (cutaneous, rabbit). Furthermore, p-cresol, but neither o- nor m-cresol, produced permanent pigment loss in the hair of mice (1).

2.4 Other Toxic Effects

Chronic poisoning from absorption of cresols through the skin,

mucous membranes or respiratory tract has not been well studied. Campbell (2) presented incomplete studies showing that exposure of mice to an atmosphere saturated with cresylic acid vapors for 1 hr/day on consecutive days caused irritation of the nose and eyes, and death in some animals. Uzhdavini et al. (3) performed poorly documented studies on the chronic effects of o-cresol inhalation. In mice, they found evidence for: tail necrosis; slowed weight gain; cellular degeneration of the CNS; respiratory tract hyperemia, edema, proliferation of cellular elements, and hemorrhagic patches; myocardial fiber degeneration; and protein deposits in liver and kidney cells. In rats, they reported alterations in a conditioned reflex, and alterations in both peripheral blood and bone marrow elements.

The Threshold Limit Value established by the ACGIH for cresols is 5 ppm (G11).

2.5 Carcinogenicity

o, m, and p-Cresol have been reported to promote the carcinogenicity of dimethylbenzanthracene (DMBA) in skin tests with mice (4). They were slightly less active as promoters than phenol in this experiment (see table below).

Promoter*	No. mice survivors/ original no.	Avg. no. papillomas per survivor	% survivors with papilloma
Benzene Control	12/12	0	0
20% phenol	22/27	1.50	64
20% o-cresol	17/27	1.35	59
20% m-cresol	14/29	0.93	50
20% p-cresol	20/28	0.55	35

* Initiator: 0.3% DMBA in acetone. Promoter in benzene. Data at 12 weeks.

No carcinogenicity tests conducted with cresols alone have been found in the searched literature.

2.6 Mutagenicity

In onion root tips, however, m- and p-cresol produced cytological abnormalities including stickiness, erosion, pycnosis, C-mitosis, polyphoidy, and chromosome fragmentation(5). o-Cresol did not appear as active (5). These chromosomal effects do not necessarily imply that the cresols will have genetic activity in mammals. No other mutagenicity studies were found in the searched literature.

2.7 Teratogenicity

No systematic studies of the teratogenic potential of the cresols have been found. The only information available is on the effect of m-cresol on embryos of a toad (Xenopus laevis) at the neural tube stage of development (6). Concentrations of 20 to 80 ppm, m-cresol caused two developmental abnormalities: edema and tail flexion.

2.8 Metabolic Information

Very little is known about the metabolic fate of cresols in mammals. One study showed that the cresols are excreted in rabbit urine primarily as oxygen conjugates: 60-72% as ether glucuronides and 10-15% as ethereal sulphates (7). Paper chromatography showed that o- and m-cresol are hydroxylated and that p-cresol forms p-hydroxybenzoic acid (7). p-Cresol glucuronide was isolated from the urine of rabbits dosed by stomach tube with p-cresol, whereas o- and m-cresol were metabolized to 2,5-dihydroxytoluene (7). No studies have been traced of the biological effect of these and other possible metabolites of the cresols.

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No. 55

Crotonaldehyde

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

CROTONALDEHYDE

SUMMARY

Crotonaldehyde is not expected to be overly persistent in water or the atmosphere. It is not expected to bioconcentrate. It has been detected in finished drinking water and in sewage treatment plant effluents.

An increased incidence of malignant neoplasms has been observed in workers at an aldehyde factory who were exposed to crotonaldehyde, among other substances. There is, however, no indication that crotonaldehyde was the causative factor in the excess incidence of cancer.

Pathologic change was observed in the testes of mice receiving crotonaldehyde in the drinking water (0.2 g/l) for one month.

I. INTRODUCTION

Crotonaldehyde ($CH_3CH=CHCHO$; molecular weight 70.1) is a water-white, mobile liquid with a pungent, suffocating odor (Hawley, 1977). It has the following physical/chemical properties (U.S. EPA, 1979a; Hawley, 1977):

Boiling Point:	102°C
Melting Point:	-60°C
Vapor Pressure:	19 mm Hg at 20°C
Solubility:	very soluble in water; also soluble in many organic solvents.

A review of the production range (includes importation) statistics for crotonaldehyde (CAS No. 4170-30-3) which was listed in the initial TSCA Inventory (1979b) has shown that between 1 million and 8 million pounds of this chemical were produced/imported in 1977.*/

Crotonaldehyde is used as an intermediate in the manufacture of n-butanol and crotonic and sorbic acids; solvent in the purification of mineral oil; intermediate in resin and rubber antioxidant manufacture; and in organic syntheses (NCI, 1978). Other uses are as a warning agent in fuel-gas, insecticides, leather tanning, production of rubber accelerators, and as an alcohol denaturant (Hawley, 1977).

II. ENVIRONMENTAL FATE

Formaldehyde, the simplest aldehyde, is almost entirely hydrated in water, thus it is nonvolatile and is inactive toward photochemical dissociation. Higher aldehydes, such as crotonaldehyde, are less hydrated in water, more volatile, and somewhat active toward photochemical degradation (Calvert and Pitts, 1966). Crotonaldehyde is expected to be oxidized in water at the double bond to form keto aldehydes and cleavage products (U.S. EPA, 1977). Crotonaldehyde biodegrades at a slow to moderate

*/ This production range information does not include any production/importation data claimed as confidential by the person(s) reporting for the TSCA Inventory, nor does it include any information which would compromise Confidential Business Information. The data submitted for the TSCA Inventory, including production range information, are subject to the limitations contained in the Inventory Reporting Regulations (40 CFR 710).

rate; acclimated bacteria can speed the degradation rate (U.S. EPA, 1979a). In general, neither crotonaldehyde nor its oxidation products are expected to be overly persistent in water (U.S. EPA, 1977).

In air, aldehydes are expected to photodissociate to RCO and H atoms rapidly and competitively with their oxidation by HO radical. The projected half-life is on the order of 2 to 3 hours (Calvert and Pitts, 1966). Oxidation of crotonaldehyde by HO radical should result in addition at the double bond to form a keto aldehyde (U.S. EPA, 1977). Crotonaldehyde is a reactive component of auto exhaust and may contribute to smog (Dimitriades and Wesson, 1972).

B. Bioconcentration

Crotonaldehyde is not expected to bioconcentrate (based on its similarity to acrolein) (U.S. EPA, 1977).

C. Environmental Occurrence

Crotonaldehyde has been detected in finished drinking water, sewage treatment plant effluents (U.S. EPA, 1976), in wastewater used for irrigation of potatoes (Dodolina et al., 1976), and the atmosphere (IARC, 1976).

Crotonaldehyde occurs naturally in essential oils extracted from the wood of oak trees (Egorov, 1976). It has also been found in the volatiles from cooking mutton (Nixon et al., 1979) and in tobacco and tobacco smoke constituents (Pilott, 1975).

III. PHARMACOKINETICS

Although no information was found specifically on the metabolism of crotonaldehyde, it is probably oxidized to an acid and subsequently to CO_2 in the same manner as other small aliphatic aldehydes. Crotonaldehyde is a potential alkylating agent by the metabolic formation of an activated epoxy derivative at the double bond and via reaction with amino groups of cellular macromolecules (NCI, 1978).

IV. HEALTH EFFECTS

A. Carcinogenicity

An increased incidence of malignant neoplasms has been observed in workers at an aldehyde factory who were exposed to acetaldehyde, butyraldehyde, crotonaldehyde, aldol, several alcohols, and longer chain aldehydes. Crotonaldehyde was found in concentrations of 1-7 mg/m^3. Of the 220 people employed in this factory, 150 had been exposed for more than 20 years. During the period 1967 to 1972, tumors were observed in nine males (all of whom were smokers). The tumor incidences observed in the workers exceeded incidences of carcinomas of the oral cavity and bronchogenic lung cancer expected in the general population and, for the age group 55-59 years, the incidence of all cancers in chemical plant workers. There is no indication that crotonaldehyde was the causative ractor in the excess incidence of cancer (Bittersohl, 1974, 1975).

B. Mutagenicity

Schubert (1972) reported chromosome breakage in human lymphocytes exposed to crotonaldehyde *in vitro*. When tested in *Salmonella typhimurium* (tester strains TA1535, TA1537, TA1538, TA100, and TA98) both in the presence and absence of a metabolic activation system, crotonaldehyde was nonmutagenic. It also failed to increase the incidence of mitotic recombination in *Saccharomyces cerevisiae* D3 in the presence and absence of a metabolic activation system (NCI, 1978).

C. Reproductive Effects

Pathologic change was observed in the testes of mice one month following a single intraperitoneal injection of crotonaldehyde (1 mg/mouse). In a related study, similar changes were observed in the testes of mice receiving crotonaldehyde in the drinking water (0.2 g/l) for one month (Auerbach *et al.*, 1977; Moutschen-Dahmen *et al.*, 1975; Moutschen-Dahmen *et al.*, 1976).

D. Other Toxicity

Skog (1950) studied the effects of lower aliphatic aldehydes in rats and mice. When administered subcutaneously or by inhalation, crotonaldehyde caused lung edema and mild narcosis. Death was delayed and probably resulted from the lung damage.

With cats, similar effects were seen, with death due to lung edema or bronchial pneumonia occurring within 24 hours for injection and between 6 and 48 hours for inhalation studies (Skog, 1950).

The oral LD_{50} for crotonaldehyde in the rat is 300 mg/kg; the 30-minute LC_{50} in the rat is 4000 mg/kg. The rabbit dermal LD_{50} is 380 mg/kg (NIOSH, 1979).

E. Other Relevant Information

A case of apparent sensitization to crotonaldehyde has been reported in a laboratory worker who handled "small" amounts of the material (ACGIH, 1971).

Crotonaldehyde is a strong mucous membrane irritant (NIOSH, 1978).

V. AQUATIC EFFECTS

The 96-hour LC_{50} (partial flow-through system) for crotonaldehyde in bluegill sunfish is 3.5 ppm; in tidewater silversides the 96-hour LC_{50} is 1.3 ppm (Dawson, 1975/1977).

VI. EXISTING GUIDELINES

The OSHA standard for crotonaldehyde in air is a time weighted average (TWA) of 2 ppm (39CFR23540).

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No. 56

Cyanides

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

CYANIDES

SUMMARY

Cyanide is well-known as an acute, rapidly acting poison which has caused numerous deaths, primarily in occupational situations. The mechanism of cyanide intoxication is attributable to the biochemical inhibition of cellular respiration, which produces a condition resembling acute hypoxia. Despite the considerable potency of cyanide as an acute poison, repeated sublethal exposures do not result in cumulative adverse effects in animals or man. In a chronic feeding study in rats, a no observable adverse effect level (NOAEL) was found to be 12 mg/kg/day. Extrapolation of this value to humans, using the application of a safety factor of 100, results in an acceptable daily intake for man (ADI) of 8.4 mg.

Cyanide exists in water in the free form (CN^- and HCN), which is extremely toxic, or in a form bound to organic or inorganic moieties which is less toxic. Cyanide is lethal to freshwater fishes at concentrations near 50 µg/l and has been shown to adversely affect invertebrates and fishes at concentrations near 10 µg/l. Very few saltwater data have been generated. Cyanide affects fish and invertebrates by inhibiting utilization of available oxygen for metabolism at the cellular level of respiration.

CYANIDES

I. INTRODUCTION

This profile is based primarily upon the Ambient Water Quality Criteria Document for Cyanides (U.S. EPA, 1979). The National Institute for Occupational Safety and Health (NIOSH, 1976) has also prepared a recent comprehensive review of health hazards associated with hydrogen cyanides (HCN) and commercially important cyanide salts (NaCN, KCN, and $Ca(CN)_2$).

The toxicologic effects of cyanides are based upon their potential for rapid conversion by mammals to HCN. Cyanide production in the United States is now over 700 million pounds per year and appears to be increasing steadily (Towill, et al. 1978). The major industrial users of cyanide in the United States are the producers of steel, plastics, synthetic fibers and chemicals, and the electroplating and metallurgical industries (NIOSH, 1976; Towill, et al. 1978).

II. EXPOSURE

A. Water

Cyanide exists in water in the free form (CN^- and HCN), or bound to organic or inorganic moieties. Cyanide is not commonly found in United States water supplies. Among 2,595 water samples tested, the highest cyanide concentration found was 8 ppb (Towill, et al. 1978). The volatility of HCN, the predominant form in water, accounts in part for the low levels usually measured. The U.S. EPA (1979) has estimated the bioconcentration factor of cyanide at 2.3.

B. Food

Except for certain naturally occurring organonitriles in plants (e.g., cyanogenic glycosides, such as amygdalin), it is uncommon to find cyanide in foods.

C. Ambient Air

There is insufficient information available to estimate population exposures to cyanide via ambient air (U.S. EPA, 1979).

III PHARMACOKINETICS

A. Absorption

The common inorganic cyanides are rapidly absorbed across the skin (Drinker, 1932; Potter, 1950; Tovo, 1955; Walton and Witherspoon, 1926), stomach and duodenum, and lungs (Goesselin, et al. 1976). Quantitative estimates of the rate of penetration by various routes of exposure are unavailable, however. The rapid absorption of cyanide is evidenced by the fact that death may be produced within a matter of minutes following inhalation or ingestion.

B. Distribution

Cyanide is distributed to all organs and tissues via the blood, where its concentration in red cells is greater than that in plasma by a factor of two or three. This may be due, at least in part, to a preferential binding of cyanide to methemoglobin (Smith and Olson, 1973). Although quantitative data are lacking, it is predicted that cyanide may readily cross the placenta.

C. Metabolism

By far, the major pathway for the metabolic detoxification of cyanide involves its conversion to thiocyanate via the enzyme rhodanase (deDuve, et al. 1955). A minor pathway for cyanide metabolism involves nonenzymatic conjugation with cysteine, a reaction which accounts for no more than 15 percent of cyanaide metabolism in the rat (Wood and Cooley, 1956). Very small amounts of cyanide can be excreted unchanged (as HCN) or converted to carbon dioxide (Friedberg and Schwarzkopf, 1969).

D. Excretion

Among rats given 30 mg of sodium cyanide intraperitoneally over eight days, it was estimated that 80 percent of the total dose was excreted in the urine in the form of thiocyanate (Wood and Cooley, 1956). Cyanide does not appear to accumulate significantly in any body compartment with chronic exposures.

IV. EFFECTS

A. Carcinogenicity

Pertinent data confirming the carcinogenicity of cyanide were not found in the available literature.

B. Mutagenicity

Pertinent data concerning the mutagenicity of cyanide were not found in the available literature.

C. Teratogenicity

Cyanide is not known to be teratogenic. However, thiocyanate, the major metabolic product of cyanide in vivo,

has produced developmental abnormalities in the chick (Nowinski and Pandra, 1946) and ascidian embryo (Ortolani, 1969) at high concentrations.

D. Other Reproductive Effects

Pertinent information regarding the possible effect of cyanide on fertility or reproductive success was not found in the available literature.

E. Chronic Toxicity

Human inhalation of 270 ppm HCN brings almost immediate death, while 135 ppm is fatal after 30 minutes of exposure (Dudley, et al. 1942). The mean lethal dose of HCN and its alkali metal salts by ingestion in humans is in the range of 50 to 200 mg (1 to 3 mg/kg), with death coming in less than one hour (Gosselin, et al. 1976). In non-fatal poisonings, recovery is generally rapid and complete. The mechanism of acute cyanide intoxication can be attributed to the biochemical inhibition of cytochrome c oxidase, the terminal enzyme complex in the respiratory electron transport chain of mitochondria (Gosselin, et al. 1976). The major feature of cyanide poisoning resembles the effects of acute hypoxia, which results in a decreased utilization of oxygen by the tissues. Cyanide poisoning differs from other types of hypoxia in that the oxygen tension in peripheral tissues usually remains normal or may even be elevated (Brobeck, 1973).

Despite the high lethality of large single doses or acute inhalation exposures to high vapor concentrations

of cyanide, repeated sublethal doses do not result in cumulative adverse effects (Hertting, et al. 1960; Hayes, 1967; American Cyanamid, 1959).

F. Other Relevant Information

Since cyanide acts by inhibiting cytochrome c oxidase, it is reasonable to assume that any other inhibitor of the same enzyme (e.g. sulfide or azide) would have toxic effects synergistic with (or additive to) those of cyanide. This has not been demonstrated experimentally, however.

Cyanide poisoning is specifically antagonized by any chemical agent capable of rapidly generating methemoglobin *in vivo*, such as sodium nitrite, or other aromatic nitro and amino compounds (Smith and Olson, 1973).

V. AQUATIC TOXICITY

A. Acute Toxicity

There have been numerous studies investigating the toxicity of cyanide in freshwater fish. Free cyanide concentrations in the range of about 50 to 200 µg/l have eventually proven fatal to most species. Certain life stages and species of fish appear to be more sensitive to cyanide than others. Eggs, sac fry, and warmwater species tended to be the most resistant.

Several authors have reported increased cyanide toxicity with the reduction of dissolved oxygen or with a rise in water temperature. However, water alkalinity, hardness, and pH below 8.3 have not been shown to have a pronounced effect on the acute toxicity of cyanide to fish. The reported range for LC_{50} values for freshwater fish is

from 52 µg/l, for juvenile brook trout, to 507 µg/l, for sac fry brook trout, Salvelinus fontinalis. For the freshwater invertebrates, the results from 11 acute tests on 6 species have shown a range of LC_{50} values from 83 µg/l for cladoceran, Daphnia pulex to 760,000 µg/l for snail, Goniobasis livescens.

The only saltwater species to be studied is the oyster. A short exposure of an oyster to cyanide resulted in supression of activity after 10 minutes of exposure to 150 µg/l (U.S. EPA, 1979).

B. Chronic Toxicity

Based on long-term tests with bluegills (embryo-larval) and reproduction by brook trout and fatheads, the geometric mean of the chronic effect level concentrations is 9.6 µg/l (Koenst, et al. 1977; Lind, et al. 1977; Kimball, et al. 1978). Life cycle tests on the scud, Gammarus pseudolimnaeus, and the isopod, Ascellus communis, show the chronic values to be 18.3 and 34.1 µg/l, respectively (U.S. EPA, 1979). The chronic toxicity of cyanide in marine species has not been reported.

C. Plant Effects

In the only plant test reported, 90 percent of the blue-green alga, Microcystis aerusinoss, was killed when exposed to a free cyanide concentration of 7,790 µg/l (Fitzgerald, et al. 1952).

There was an inhibition of respiration in the marine alga, Prototheca zopfi, at 3,000 µg/l and enzyme

inhibition in Chlorella sp. at 30,000 µg/l (Webster and Hackett, 1965; Nelson and Tolbert, 1970).

D. Residue

No residue data is available for cyanide toxicity in either salt or freshwater species. The U.S. EPA (1979) has estimated the bioconcentration factor of cyanide to be 2.3.

VI EXISTING GUIDELINES AND STANDARDS

Neither the human health nor aquatic criteria derived by U.S. EPA, 1979, which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will change.

A. Human

The U.S. Public Health Service Drinking Water Standards of 1962 established 0.2 mg CN^-/l as the acceptable level for water supplies. A similar criterion has been adopted by the Canadian government (Health and Welfare Canada, 1977). In addition to defining the 0.2 mg CN^-/l criterion, the U.S. Public Health Service (1962) has set forth an "objective" of 0.01 mg CN^-/l in water, "because proper treatment will reduce cyanide levels to 0.01 mg/l or less."

The U.S. Occupational Safety and Health Administration (OSHA) has established a permissible exposure limit for KCN and NaCN at 5 mg/m^3 as an eight-hour, time-weighted average. The National Institute for Occupational Safety and Health (NIOSH) recommends 5 mg/m^3 as a ten minute ceiling for occupational exposure to KCN and NaCN.

The OSHA permissible limit for exposure to HCN is 10 ppm (11 mg/m^3) as an eight-hour time-weighted average. NIOSH recommends 5 mg/m^3 as a ten minute ceiling level for exposure to HCN.

Based upon the results of a two year chronic feeding study in rats, the U.S. EPA (1979) has calculated an acceptable daily intake (ADI) of cyanide for man to be 8.4 mg/kg. This value was derived from the no observable adverse effect level (NOAEL) for rats of 12 mg/kg/day and the application of a safety factor of 100. The corresponding draft water quality criterion derived from these data is 4.11 mg/l. However, the U.S. EPA (1979) has recommended that the U.S. Public Health Service Drinking Water Standard of 200 µg/l be retained as a safe level for man.

B. Aquatic

For free cyanide (expressed as CN), the draft criterion to protect freshwater aquatic life is 1.4 µg/l as a 24-hour average, and the concentration should not exceed 38 µg/l at any time (U.S. EPA, 1979).

Draft saltwater criterion is not available for cyanide toxicity, because of the paucity of valid data (U.S. EPA, 1979).

CYANIDES

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No. 57

Cyanogen Chloride

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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CYANOGEN CHLORIDE

I. INTRODUCTION

Cyanogen chloride is a colorless gas at room temperature with a molecular weight of 61.48, a melting point of -6.5°C, a boiling point of 13.8°C, and a specific gravity of 1.186. It is soluble in alcohol or ether, and slightly soluble in water. (Int. Tch. Inf. Inst., 1978).

Cyanogen chloride is used as a fumigant, metal cleaner, in ore refining, production of synthetic rubber and in chemical synthesis (Arena, 1974). Cyanogen chloride can be used in the military as a poison gas.

II. EXPOSURE

The major sources of exposure to cyanogen chloride are in the above mentioned industrial uses. The potentiality of cyanogen chloride as a water pollutant has not been described in the available literature.

III. PHARMACOKINETICS

The toxicity of cyanogen chloride resides very largely on its pharmacokinetic property of yielding readily to hydrocyanic acid (also called hydrogen cyanide or prussic acid) in vivo. The red cells of whole blood rapidly convert cyanogen chloride to cyanide, while serum destroys cyanogen chloride without forming hydrocyanic acid (Aldridge and Evans, 1946).

Reference should be made to the EPA/ECAO Hazard Profile for cyanides (U.S. EPA, 1979) for a general discussion on absorption, distribution, metabolism and excretion. Cyanogen chloride, like HCN, is metabolically converted to thiocyanate (HCNS) (Aldridge and Evans, 1946).

IV. EFFECTS

A. Carcinogenicity, Mutagenicity, Teratogenicity, and Other Reproductive Effects

Pertinent information could not be located in the available literature.

B. Chronic Toxicity

Inhaling small amounts of cyanogen chloride causes dizziness, weakness, congestion of the lungs, hoarseness, conjunctivitis, loss of appetite, weight loss, and mental deterioration. These effects are similar to those found from inhalation of cyanide (Dreisbach, 1977). Cyanogen chloride is an irritant to both eyes and throat (Int. Tech. Inf. Inst., 1978).

Cyanogen chloride acts as a chemical asphyxiant, releasing cyanide which causes internal asphyxia by inhibiting cellular respiration. Cyanohemoglobin may also be formed slowly, but the toxicity is mainly due to the inhibition of cytochrome oxidase, an enzyme which utilizes molecular oxygen for cell respiration (Dreisback, 1977).

C. Acute Toxicity

Ingestion or inhalation of a lethal dose of cyanogen chloride (LD_{50} = 13 mg/kg), as for cyanide or other cyanogenic compounds, causes dizziness, rapid respiration, vomiting, flushing, headache, drowsiness, drop in blood pressure, rapid pulse, unconsciousness, convulsions with death occurring within 4 hours (Dreisbach, 1977).

By subcutaneous route, the LD_{LO} for cyanogen chloride are as follows: mouse, 39 mg/kg; dog, 5 mg/kg; and rabbit, 20 mg/kg. By inhalation, an LC_{LO} in the dog was found to be 79 ppm/8 hours. Also by inhalation, the LC_{50}'s in terms of ppm for 30 minute exposures are: rat, 118; mouse, 177; rabbit, 207; and guinea pig, 207 (Int. Teh. Inf. Inst., 1978).

V. AQUATIC TOXICITY

Pertinent information could not be found in the available literature pertaining to the toxic effects of cyanogen chloride to aquatic organisms. The reader is referred to EPA/ECAO Hazard Profile for cyanides (U.S. EPA, 1979).

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

Threshold limit values for cyanogen chloride have been set at 0.3 ppm and 0.6 mg/m^3 for an 8-hour workday. (ACGIH, 1979).

CYANOGEN CHLORIDE

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No. 58

DDD

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DDD

Summary

DDD can exist in two forms, the o,p'- or the p,p'-isomers. p,p'-DDD [1,1-(2,2-dichloroethylidlene)-bis-4-chlorobenzene] is a contaminant (~0.3%) of commerical preparations of DDT [1,1'-(2,2,2-trichloroethylidene)-bis-4-chlorobenzene] as well as being a metabolite of DDT. It has also been used as an insecticide in its own right under the names TDE or Rhothane. p,p'-DDD is the first metabolite of p,p'-DDT leading to the eventual elimination of p,p'-DDT from the body as p,p'-DDA [2,2-bis(4-chlorophenyl) acetic acid]. The residency time of DDD in the body is relatively short. There is some evidence that DDD is carcinogenic in mice; however, in other species, it appears to be non-carcinogenic. p,p'-DDD has been shown to be mutagenic in Drosophila, but not in yeast or bacteria. In cell culture, p,p'-DDD causes chromosomal breaks.

The only available p,p'-DDD toxicity data involves saltwater fish and invertebrates and freshwater invertebrates. The 96-hour LC_{50} value for two invertebrates and three fish range from 1.6 to 42.0 µg/l. p,p'-DDD appears to be one-fifth to one-seventh as acutely toxic as p,p'-DDT.

DDD

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for DDT (U.S. EPA, 1979a).

DDD is a contaminant of technical p,p'-DDT [1,1'-(2,2,2-trichloroethylidene)-bis-4-chlorobenzene]. It has also been utilized as an insecticide in its own right under the common names TDE or Rhothane. Its two isomers, p,p'-DDD [1,1'-(2,2-dichloroethylidene)-bis-4-chlorobenzene] and o,p'-DDD, make up approximately 0.3 and 0.1 percent, respectively, of technical DDT. Between 1970 and 1973 (the EPA banned DDT in 1972), a significant drop in residues of DDD and DDT occurred in the U.S.A., constituting decreases of 89 and 86 percent, respectively.

II. EXPOSURE

Little information is available on exposure to DDD, although the general exposure pattern probably follows that of DDT, as outlined in DDT: Hazard Profile (U.S. EPA, 1979b). DDD appears to be disappearing from the U.S. environment at approximately the same rate as DDT as a result of the 1972 ban on DDT (U.S. EPA, 1975). Wessel (1972) calculated the daily intake of p,p'-DDD to be 0.012 mg/man/day; this was about half the daily intake of p,p'-DDT.

III. PHARMACOKINETICS

A. Absorption

Pertinent data could not be located in the available literature.

B. Distribution

The distribution of DDD is the same as that described for DDT in DDT: Hazard Profile (U.S. EPA, 1979b). The human adipose storage of DDD is less than that of either DDT or DDE [1,1'-(2,2-dichloroethenylidene)-bis-4-chlorobenzene].

C. Metabolism

p,p'-DDD is the first metabolite in the multistep pathway of converting p,p'-DDT to p,p'-DDA [2,2-bis(4-chlorophenyl)-acetic acid], the metabolite which is eventually excreted by rats and by man (Peterson and Robinson (1964). Urinary p,p'-DDA excretion and serum DDD concentrations showed increases with DDT dosage in man and declined after dosing ended (Morgan and Roan, 1977). The enzymes for converting p,p'-DDT to p,p'-DDD are present in all tissues, while the enzymes for further metabolism of DDD appear to be absent in brain, heart, pancreas, and muscle of rats (Fang, et al. 1977).

D. Excretion

Doses of o,p'-DDD yield o,p'-DDA and ring hydroxylation products of o,p'-DDA in the urine and feces of rats in addition to serine and glycine conjugates in urine (Reif and Sinsheimer, 1975).

DDD is further metabolized to DDA, which is excreted in the urine (U.S. EPA, 1979a).

IV. EFFECTS

A. Carcinogenicity

Only two studies have been performed to assess the carcinogenicity of p,p'-DDD. In a lifespan study, CF1 mice were fed 37.5 mg/kg/day DDD in their diet (Tomatis, et al. 1974). DDD-exposed animals showed slight increases in liver tumors in males only, but lung adenomas were markedly increased in both sexes. In a National Cancer Institute study (1978), Osborne-Mendel rats and B6C3F1 mice were dosed with p,p'-DDD for 78 weeks. In rats, DDD had no carcinogenic effects in the females, (43 or 85 mg/kg/day), but caused a significant increase of follicular cell adenomas in the low dose males (82 mg/kg/day). Carcinomas of the thyroid were also observed. Be-

cause of high variation of thyroid lesions in control male rats, these findings are considered only suggestive of a chemical-related effect. In mice, p,p'-DDD was not carcinogenic.

B. Mutagenicity

p,p'-DDD has been shown to be non-mutagenic in E. coli Pol-A strains (Fluck, et al. 1976) and Escherichia marcescens (Fahrig, 1974). The only positive result found in any of the bacterial test systems was reported by Buselmaier, et al. (1972) upon the administration of p,p'-DDD to mice and assaying for back mutation of Salmonella typhimurium and E. marcescens following incubation in the peritoneum in the host-mediated assay. Yeast host mediated assays using Saccharomyces cerevisiae were negative (Fahrig, 1974), along with an X-linked recessive lethal assay in Drosphila melanogaster (Vogel, 1972). In mammalian systems, the mutagenic activity of p,p'-DDD is relatively weak. This is evidenced by the fact that, depending upon the dose and route of administration and the species sensitivity of the test organism, reported studies are negative or marginally positive (U.S. EPA, 1979a). Some chromosomal aberrations and inhibition of proliferation have been observed with p,p'-DDD in cell culture (Palmer, et al. 1972; Mahr and Miltenburger, 1976). The o,p'-isomer is less active with regard to chromosome damage (Palmer, et al. 1972).

C. Teratogenicity, Other Reproductive Effects, and Chronic Toxicity

Pertinent data could not be located in the available literature.

D. Other Relevant Information

Since DDD is a metabolite of DDT, as well as a contaminant of commercial preparations of DDT, many of the effects of DDT could be mediated through DDD. Information on DDT is presented in DDT: Hazard Profile (U.S. EPA, 1979b).

V. AQUATIC TOXICITY

A. Acute Toxicity

The most insensitive freshwater invertebrate was the scud, Gammarus lacustris, with a 96-hr. LC_{50} static value of 0.60 µg/L (Sanders, 1969). Of the Cladoceran, the Daphnia pulex species was the most sensitive with a static LC_{50} of 3.2 µg/l, while the Simocephalus serrulatus was the least sensitive with a LC_{50} of 5.2 µg/l (Sanders and Cope, 1966). p,p'-DDD toxicity has been investigated for several saltwater species. LC_{50} values for two invertebrates, the Eastern oyster, Crassostrea virginica, and the Korean shrimp, Palaemon macrodactylus (Schoettger, 1970), are 25 µg/l and 1.6 µg/l, respectively, in 96-hr flow-through exposures. In flow-through exposures to three species of saltwater fish, 96-hr LC_{50} values range from 2.5 to 42 µg/l for the stripped bass, Morone saxatilis, Korn and Earnest, 1974). Two species, Morone saxatilis (Korn and Earnest, 1974) and Fundulus similis (U.S. EPA, 1979a), were exposed to both p,p'-DDD and p,p'-DDT under similar conditions. A comparison of the results indicates that p,p'-DDD is one-fifth to one-seventh as acutely toxic to these species as is p,p'-DDT. However, four to five week old tadpoles of the freshwater toad (Bufo woodhuusei fowleri) were much more sensitive, having 96-hr. LC_{50} values of 160 µg/l compared with 1,000 µg/l for p,p'-DDT. The DDT sensitivity increased with age (Sanders, 1970).

B. Chronic Toxicity, Plant Effects and Residues

Pertinent data could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

In 1972, the U.S. EPA banned the agricultural use of DDT in the United States. There are no other specific guidelines or standards for DDD. However, for the protection of human health with respect to DDD, criteria of 0.98, 0.098, and 0.0098 ng/l have been proposed for DDT corresponding to risk levels of 10^{-5}, 10^{-6}, and 10^{-7}, respectively. If water alone is consumed, the water concentration should be less than 0.36 µg/l to keep the lifetime cancer risk below 10^{-5}.

B. Aquatic

The criteria for DDT and its metabolites are proposed for the protection of aquatic life from the effects of DDD. The 24-hour average for the protection of freshwater aquatic life is 0.00023 µg/l, not to exceed 0.41 µg/l at any time. For saltwater aquatic life, the 24-hour average is 0.0067 µg/l, not to exceed 0.021 µg/l at any time.

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No. 59

DDE

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

DDE

Summary

DDE exists as two isomers, o,p'- and p,p'-DDE [1,1'-(2,2-dichloroethenylidene)-bis-4-chlorobenzene] is the major contaminant (ca. 4 percent) of commercial preparations of p,p'-DDT [1,1'-(2,2,2-trichloroethylidene)- bis-4-chlorobenzene], as well as being a metabolite of p,p'-DDT. p,p'-DDE is a highly lipophilic compound which undergoes no further metabolism. Its residency time in the body is extremely long. p,p'-DDE has been shown to be carcinogenic in mice but not in rats. In cell culture it causes chromosomal breaks.

The only aquatic toxicity data available on p,p'-DDE involve acute toxic flow-through exposures to two saltwater invertebrates. The 48-hr. LC_{50} for a shrimp is 28 µg/l; the 96-hr. LC_{50} for the Eastern oyster is 14 µg/l.

DDE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for DDT and metabolites (U.S. EPA, 1979a).

DDE is a contaminant of technical 1,1'-(2,2,2-trichloroethylidene)-bis-4-chlorotenzene (DDT). Its two isomers, p,p'-DDE [1,1'-(2,2-dichloroethenylidene)-bis-4-chlorobenzene] and o,p'-DDE make up approximately 4.0 and 0.1 percent, respectively, of technical grade DDT. Between 1970 and 1973 (the EPA banned DDT in 1972), a significant drop in the residues of DDT in the U.S. occurred, constituting a decrease of 86 percent. However, during this time period, residues of DDE decreased only 27 percent. In fact, p,p'-DDE residues comprise most of the biological residues (ca. 71 percent) arising from DDT application (U.S. EPA, 1979a; Kveseth, et al. 1979).

II. EXPOSURE

Little information is available on exposure to DDE, although the general exposure pattern probably follows that of DDT, as outlined in DDT: Hazard Profile (U.S. EPA, 1979b). DDE residues appear to be disappearing from the environment at a slower rate than DDT following the 1972 ban on DDT (U.S. EPA, 1975). Wessel (1972) calculated the daily dietary intake of p,p'-DDE to be 0.018 mg/man/day, as compared with a value of 0.027 mg/man/day for DDT. A recent study by de Campos and Olszyne-Marzys (1979) based on studies in Latin American countries still using DDT indicates that human milk contains more p,p'-DDE than p,p'-DDT (up to 3 µg/l whole milk) in every sample taken.

III. PHARMACOKINETICS

A. Absorption

DDE is absorbed from the gastrointestinal tract with high efficiency characteristic of dietary fat. Maximum lipid solubilities reach 100,000 ppm.

B. Distribution

The distribution of DDE is similar to that described for DDT in the EPA/ECAO Hazard Profile on DDT (U.S. EPA, 1979b). Serum and adipose concentrations of p,p'-DDE rise slower than DDT, with the peak some months in following termination of dosing. The human adipose storage of p,p'-DDE is greater than that for DDT, and p,p'-DDE is eliminated from the body very slowly. This is also true for the Rhesus monkey (Durham, et al. 1963). Storage loss data predict that, if dietary intake were eliminated, it would take an entire lifespan to eliminate the average human body burden of p,p'-DDE. It has been shown that tissue storages of p,p'-DDE in the general population originate almost entirely from dietary p,p'-DDE rather than DDT conversion (U.S. EPA, 1979a). However, this may not be the case for p,p'-DDE residues in human milk (de Campos and Olszyne-Marzys, 1979).

C. Metabolism

The end product of the metabolism of DDT which proceeds via reductive dehydrochlorination is p,p'-DDE. In addition, p,p'-DDE is the major storage product of DDT in animals [apart from hamsters (Agthe, et al. 1970)] and humans. The enzymes for metabolizing DDT to p,p'-DDE are present in all tissues (Fang, et al. 1977).

In humans given p,p'-DDT orally, no more than one-fifth of the absorbed DDT ultimately undergoes conversion to p,p'-DDE (Morgan and Roan, 1977). p,p'-DDE does not undergo further metabolism to 2,2-bis(4-chlorophenyl)-acetic acid (DDA), the urinary excretion product of DDT.

D. Excretion

Excretion of p,p'-DDE has not been demonstrated in man. In mice, p,p'-DDE is excreted in the urine (Wallcave, et al. 1974). The o,p'-isomer is more easily excreted than the p,p'-isomer (Morgan and Roan, 1977).

IV. EFFECTS

A. Carcinogenicity

Only two studies have been performed to assess the carcinogenicity of p,p'-DDE. In a lifespan study, CF-1 mice were fed 37.5 mg/kg/day p,p'-DDE in their diet (Tomatis, et al. 1974). p,p'-DDE increased liver tumor incidence from 1 percent in controls to 90 percent in treated female animals, and from 34 to 74 percent in male animals. The combination p,p'-DDE/DDD produced more tumors than either constituent alone at the same concentration in the combination. In a National Cancer Institute study (1978), Osborne-Mendel rats and B6C3F1 mice were dosed with p,p'-DDE for 78 weeks. In rats, p,p'- DDE had no carcinogenic effect on either females (22 mg/kg/day) or males (42 mg/kg/ day), although hepatotoxicity was evident. In mice, hepatocellular carcinomas were significantly increased in the animals fed p,p'-DDE (22 and 39 mg/kg/day for females and males, respectively).

B. Mutagenicity

p,p'-DDE has been shown to be nonmutagenic in E. coli Pol-A strains (Fluck, et al. 1976), Escherichia marcescens (Fahrig, 1974), and in the host mediated assay using Salmonella typhimurium and E. marcescens (Buselmaier, et al. 1972) and Saccharomyces cerevisiae (Fahrig, 1974). Vogel (1972) measured X-linked recessive lethal mutations in Drosophila melanogaster and found no activity for p,p'-DDE. In mammalian systems, the mutagenic activity of p,p'-DDE is relatively weak. This is evidenced by the fact that, de-

pending upon the dose and route of administration and the species sensitivity of the test organism, reported studies are negative or marginally positive (U.S. EPA, 1979a). Some chromosomal aberrations and inhibition of proliferation have been observed with p,p'-DDE in cell culture (Palmer, et al. 1972; Mahr and Miltenburger, 1976). The o,p'-isomer causes fewer chromosomal aberrations (Palmer, et al. 1972).

C. Teratogenicity, Other Reproductive Effects and Chronic Toxicity

Pertinent information could not be located in the available literature.

D. Other Relevant Information

Since p,p'-DDE is a metabolite of DDT, as well as a contaminant of commercial preparations of DDT, many of the effects of DDT could be mediated through p,p'-DDE. Information on DDT is presented in DDT: Hazard Profile (U.S. EPA, 1979b). Oral acute LD_{50} values for p,p'-DDE in rat are 380 mg/kg for males but 1,240 mg/kg for females (Hayes, et al. 1965).

V. AQUATIC TOXICITY

A. Acute Toxicity

The 96-hr. LC_{50} value for p,p'-DDE for the comparatively resistant freshwater planarian (Polycelis felina) was 1,050 µg/l (Kouyoumjian and Uglow, 1974). The acute toxicity of p,p'-DDE has also been investigated in two saltwater invertebrates. The 48-hr. LC_{50} for the brown shrimp, Penaeus aztecus, was 28 µg/l; the 96-hr. LC_{50} for the Eastern oyster, Crassostrea virginica, was 14 µg/l (U.S. EPA, 1979a). Both studies were flow-through exposures.

B. Chronic Toxicity and Plant Effects

Pertinent data could not be located in the available literature.

C. Residues

p,p'-DDE is a major metabolite of DDT in aquatic ecosystems. One study involving bird eggshells and DDT showed p,p'-DDE to comprise 62 percent of the DDT metabolites (U.S. EPA, 1979a). Average residues in eggshells of the great black-backed gull ranged from 14 to 68 ng/g of lipid (Cooke, 1979). p,p'-DDE in fat and muscle of the white-faced ibis in 1974/75 were as high as 65 ng/g lipid (Capen and Leiker, 1979). No studies are available, however, involving p,p'-DDE specifically.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

In 1972, the U.S. EPA banned the agricultural use of DDT in the United States. There are no other specific guidelines or standards for DDE. However, for the protection of human health with respect to DDE, criteria of 0.98, 0.098 and 0.0098 ng/l have been proposed for DDT corresponding to risk levels of 10^{-5}, 10^{-6}, and 10^{-7}, respectively. If water alone is consumed, the water concentration should be less than 0.36 µg/l to keep the lifetime cancer risk below 10^{-5}.

B. Aquatic

The criteria for DDT and its metabolites are proposed for the protection of aquatic life from the effects of DDE. The 24-hour average for the protection of freshwater aquatic life is 0.00023 µg/l, not to exceed 0.41 µg/l at any time. For saltwater aquatic life, the 24-hour average is 0.0067 µg/l, not to exceed 0.021 µg/l at any time.

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No. 60

DDT

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated DDT and has found sufficient evidence to indicate that this compound is carcinogenic.

DDT

Summary

The most commonly used DDT was a technical formulation and usually consisted of a mixture of p,p'-DDT (77.1 percent), o,p'-DDT (14 percent), p,p'-DDD (0.3 percent), o,p'-DDD (0.1 percent), p,p'-DDE (4 percent), o,p'-DDE (0.1 percent and 3.5 percent unidentified compounds. Pure DDT is the p,p'-isomer [1,1'-(2,2,2-trichloroethylidene)-bis-4-chlorobenzene]. Unless specifically identified, the term DDT will refer to the pure form. Prior to being banned in the U.S. in 1972, DDT was used extensively as a pesticide.

Due to the high lipid solubility of DDT, it has a long residency time in the body. DDT has produced adverse reproductive effects in rodents and birds, but adverse effects have not been noted in man. The lowest acute oral LD_{50} value was found for the dog (60-75 mg/kg). There is suggestive evidence that DDT might be a carcinogen, and weak evidence that it might be a teratogen. Chromosomal breaks have been observed with DDT exposure *in vitro* and *in vivo*.

DDT is acutely toxic to freshwater fish at concentrations as low as 0.8 µg/l and to invertebrates at 0.18 µg/l. Chronic toxicity has been manifested in the fathead minnow in the range of 0.37 to 1.48 µg/l. A weighted average bioconcentration factor of 39,000 has been estimated for DDT for consumed fish and shellfish. For saltwater fish and invertebrates, DDT concentrations as low as 0.2 µg/l and 0.14 µg/l, respectively, have been reported to be acutely toxic. Chronic toxicity data for saltwater organisms are not available.

DDT

I. INTRODUCTION

This profile is based primarily on the Ambient Water Quality Criteria Document for DDT (U.S. EPA, 1979a).

DDT has been used extensively world-wide for public health and agricultural programs as a broad spectrum insecticide. It has played a large role in the world-wide control of the malaria mosquito. In 1972, following an extensive review of health and environmental hazards of the use of DDT, the U.S. EPA decided to ban any further use of DDT. Prior to this, technical grade DDT had been widely used in the U.S., with a peak usage in 1959 of 80 million pounds. This amount decreased steadily to less than 12 million pounds by 1972. Since the 1972 ban, the use of DDT in the U.S. has been effectively discontinued. However, technical grade DDT is still used in many other countries and widespread contamination still occurs. Since DDD and DDE are also metabolites of DDT, it is sometimes difficult to separate contamination from metabolic accumulation. The compounds of DDT are extremely persistent and are so widespread that levels as high as 15 ppb have been detected in feed for laboratory animals (Coleman and Tardiff, 1979).

II. EXPOSURE

The primary route of human exposure to DDT is from ingestion of small amounts in the diet. Biological magnification of DDT in the food chains occurs by two routes: (1) direct absorption from contaminated water by aquatic organisms; (2) transfer of residues through sequential predator feeding. Meats, fish, poultry, and dairy products are the primary sources of DDT residues in the human diet. The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor of DDT at 39,000 for consumed fish and shellfish. Due to the banned usage of DDT in the U.S., there has been a

continual decline in the DDT residue in food. These decreases are reflected in the changing amounts of estimated dietary intake: 1965 - 0.062 mg/man/day; 1970 - 0.024 mg/man/day; 1973 - 0.008 mg/man/day (U.S. EPA, 1975). Levels of DDT found in the air are far below levels that add significantly to total human intake. Stanley, et al. (1971) sampled air in nine localities, and found DDT in the ranges of 1 ng/m^3 to 2520 ng/m^3 of air. Wolfe and Armstrong (1971) showed that industrial workers not wearing respirators could be exposed to significant levels of DDT in the air (up to 34 mg/man/hour), particularly in the formulating plants. Exposure for agricultural spray operators may be as high as 0.2 mg/man/hour (Wolfe, 1967). Dermal exposure for formulators was estimated to range from 5 to 993 mg/man/hour (Wolfe and Armstrong, 1971). Little DDT was found in the urine, however. Dermal absorption of DDT is minimal.

Dermal toxicity in rats occurs at 3,000 mg/kg (U.S. EPA, 1979a). Hayes (1966) estimated the intake of DDT to be in the following proportions: food - 0.04 mg/man/day; water - 4.6×10^{-6} mg/man/day; and air - 9×10^{-6} mg/man/day. The actual dose for the average man is now estimated to be 0.01 mg/man/day (U.S. EPA, 1979a).

III. PHARMACOKINETICS

A. Absorption

DDT is absorbed from the gastrointestinal tract with efficiency approaching 95 percent when ingested with dietary fat. In humans, Morgan and Roan (1971) showed that absorption of an oral dose of 20 mg DDT proceeded faster than transport out of the vascular compartment into tissue storage. Studies concerning the kinetics of absorption of DDT via inhalation or dermal routes were not found in the available literature.

B. Distribution

DDT has been found in virtually all body tissues, approximately in proportion to respective tissue content of extractable lipid. The adipose/blood ratios of DDT have been recently estimated to be approximately 280:1 (Morgan and Roan, 1977). DDT concentrations in body tissues were highest for fat tissue, followed by reproductive organs, the liver and kidney together, with lowest concentrations found in the brain (Tomatis, et al. 1971). Elimination of very low levels of DDT from storage proceeds much more slowly than that of the large stores of DDT accumulated by occupationally exposed workers or dosed volunteers (Morgan and Roan, 1971). The average North American adult, with 17 kg of body fat, contains approximately 25 mg of DDT. It is predicted from storage loss data that, if dietary intake were eliminated, most of the DDT would be lost within one or two decades (U.S. EPA, 1979a). Trace metals in the diet, particularly cadmium, may affect the mobilization of DDT in tissues (Ando, 1979).

C. Metabolism

The metabolism of DDT in man appears to be the same as the pathways reported by Peterson and Robison (1964) for the mouse. Generally, two separate reductive pathways produce the primary endpoint metabolites, p,p'-DDE and p,p'-DDA. The predominant conversion is of DDT to p,p'-DDD via dechlorination. This is the first product in a series which results in metabolites which are later excreted. The other primary pathway proceeds via reductive dehydrochlorination which results in the formation of p,p'-DDE the major storage product in animals and humans. Fant, et al. (1977) suggest that enzymatic activity for the dehydrochlorination and reductive dechlorination reactions transforming DDT to DDD and DDE is present in all tissues, whereas the enzymes involved in the hydrogenation and hydroxylation steps changing

DDD to DDA are absent in the brain, heart, pancreas, and muscle of the rat. Metabolic conversion of DDT to DDA proceeds more rapidly than conversion to the storage metabolite of DDE. For additional information regarding the DDT metabolites DDD and DDE, the reader is referred to the Hazard Profile for those chemicals (U.S. EPA, 1979b,c).

D. Excretion

The excretion of DDT was investigated in human volunteer studies of Hayes, et al. (1971) and Roan, et al. (1971). Urinary excretion predominated, with 13 to 16 percent of the daily dose being excreted as p,p'-DDA, and was shown to correlate with exposure levels of individuals working in a formulating plant (Ortelee, 1958). p,p'-DDE and DDT are the predominant compounds excreted and p,p'-DDD and p,p'-DDA are excreted in the least amounts (Morgan and Roan, 1977). p,p'-DDE was found in slightly higher concentrations in exposed workers versus the general population. Gut microorganisms have demonstrated a capacity for degradation of DDT to p,p'-DDD and p,p'-DDA.

IV. EFFECTS

A. Carcinogeniity

Lifetime and multigeneration exposures to DDT in the diet of rats, mice, and fish have produced significant increases in the formation of a number of tumor types (U.S. EPA, 1979a). The predominant lesion appears to be hepatoma. Also, Tomatis, et al. (1974) demonstrated that short-term exposure to technical grade DDT (37.5 mg/kg/day for 15 or 30 weeks), using CF-1 mice, resulted in an increased incidence and early appearance of hepatomas, similar to that caused by lifespan exposure. Mice appear much more susceptible than rats (U.S. EPA, 1979a) and the use of the mouse as an animal model for humans has been criticized (Deichmann, 1972). In these studies contaminants p,p'-DDD and p,p'-DDE were present, both of which have pro-

duced liver tumors in CF-1 mice (Tomatis, et al. 1974). Also, the combination of p,p'-DDD/DDE was found to produce more tumors than and equal concentration of either compound alone. Tarjan and Kemeny (1969) noted leukemias and pulmonary carcinomas in Bald-C mice fed 3 ppm DDT in the diet. Hepatomas have been observed in rainbow trout (Halver, et al. 1962).

A number of other studies have shown no significant increase in tumor formation following DDT exposure. Lifetime feeding studies with Syrian Golden Hamsters (Agthe, et al. 1970) and a number of long term feeding studies with various strains of rats have shown no significant increase in tumor incidence (Cameron and Cheng, 1951; Fitzhugh and Nelson, 1947; Radomski, et al. 1965; Deichmann, et al. 1967). In a 78-week National Cancer Institute study (1978), Osborne-Mendel rats given 16 and 32 mg/kg/day (males) or 11 and 21 mg/kg/day (females) showed no tumors. B6C3F1 mice given 3.3 and 6.6 mg/kg/day (males) or 13 and 26 mg/kg/day (females) also showed no tumor development. Durham, et al. (1963) found no liver pathology in Rhesus monkeys fed 100 mg/kg/day or less DDT for up to 7.5 years. At the present time, no evidence of neoplasia has been found in the studies performed in occupationally exposed or dosed volunteer subjects (U.S. EPA, 1979a).

B. Mutagenicity

DDT has not shown mutagenic activity in any of the bacterial test systems thus far studied: Salmonella typhimurium (McCann, et al. 1975; Marshall, et al. 1976); E. coli Pol-A strains (Fluck, et al. 1976); Bacillus subtilis (Shirasu, et al. 1976). Tests on eukaryotic yeast cells have been uniformly negative, with Fahrig (1974) using Saccharomyces cerevisiae and Clark (1974) using Neurospora crassa. Vogel (1972) and Clark (1974) found positive mutagenic activity in Drosophila melanogaster by measuring x-linked recessive lethal mutations. In mammalian systems, the mutagenic activity of

DDT is relatively weak. This is evidenced by the fact that, depending upon the dose and route of administration and the species sensitivity of the test organisms, reported studies are negative or only marginally positive (U.S. EPA, 1979a). In vivo and in vitro cytogenetic studies seem to indicate that DDT is a clastogenic (chromosome breaking) substance. The metabolites p,p'-DDE, p,p'-DDD, p,p'-DDA and p,p'-DDOH were also non-mutagenic except possibly for p,p'-DDD (U.S. EPA, 1979a). Chromosomal aberrations in cell lines of the kangaroo rat occurred more often with p,p'-isomers than o,p'-isomers (Palmer, et al. 1972).

C. Teratogenicity

Only minimal teratogenic effects have been reported following high dosages of DDT. Sprague-Dawley rats receiving 200 ppm DDT in their diet showed a significant increase in ring tail, a constriction of the tail followed by amputation, in the offspring (Ottoboni, 1969).

D. Other Reproductive Effects

Hart, et al. (1971) showed that DDT has an effect on prematurity and causes an increase in the number of fetal resorptions in rabbits given 50 mg/kg on days 7, 8, and 9 of gestation. Chronic exposure (less than 200 mg/kg) of rats and mice produced no adverse effects on survival of the offspring (Ware and Good, 1967; Ottoboni, 1969). Krause, et al. (1975) noted a damaging effect on spermatogenesis in rats following acute exposure to DDT (7,200 mg/kg). Also, DDT has been shown to possess estrogenic activity in rodents and birds (Welch, et al. 1969; Bittman, et al. 1968).

E. Chronic Toxicity

A number of pathological changes have been noted in rodents; the most consistent finding in lifetime feeding studies has been an increase in the size of liver, kidneys, and spleen; extensive degenerative changes in

the liver; and an increased mortality rate (U.S. EPA, 1979a). In contrast to the rodent models, Rhesus monkeys fed diets with up to 200 ppm DDT did not show liver histopathology, decrease in weight gain or food consumption, or clinical signs of illness (Durham, et al. 1963).

F. Other Relevant Information

DDT is a strong inducer of the mixed function oxidase system; this could potentially enhance the biological effects of other chemicals by activation, or diminish their activities through detoxification mechanisms (U.S. EPA, 1979a). Exposure to DDT has caused enhanced tumor incidence in N-fluoroenacetamide-treated rats (Weisburger and Weisburger, 1968) and decreased phenobarbital-induced sleeping times (Conney, 1967). Acute oral LD_{50} values in rats typically range from 100 to 400 mg/kg and 40 to 60 mg/kg i.v. The oral LD_{50} values in other animals are: 60 to 75 mg/kg (dogs); 250 to 400 mg/kg (rabbits); approximately 200 mg/kg (mice). For p,p'-DDE, the values are 380 and 1,240 mg/kg in male and female rats, respectively; for p,p'-DDA in rats, the values are 740 and 600 mg/kg, respectively (U.S. EPA, 1979a). Symptoms of DDT poisoning in humans include the following: convulsions, parasthesia of extremities and vomiting (at high doses), convulsions and nausea (less than 16 mg/kg), dizziness, confusion and most characteristically, tremors (Hayes, 1963). In rats, the liver shows changes at dietary doses less than 5 ppm (Laug, et al. 1950). No permanent injury to man from DDT has been recorded (U.S. EPA, 1979a).

V. AQUATIC TOXICITY

A. Acute Toxicity

The acute toxicity of DDT to freshwater organisms has been well documented. Data are available for 25 species of fish. The 96-hour LC_{50} values are available for the following freshwater fish: rainbow trout (Sal-

mo gairdneri), 1.7 to 42 µg/l; fathead minnow (Pimephales promelas), 7.4 to 58 µg/l; channel catfish (Ictalurus punctatus), 16 to 17.5 µg/l; bluegill (Lepomis macrochirus), 1.2 to 210 µg/l. The most sensitive of fish was the yellow perch (Perca flavescens) with a 96-hour LC_{50} of 0.6 µg/l (Marking, 1966). Invertebrate freshwater species are more sensitive than fish. For Daphnia magna, 48-hour LC_{50} values of 1.48 µg/l have been reported (Priester, 1965). One week old crayfish (Orconectus nais) had a 96-hour LC_{50} value of 0.18 µg/l (Saunders, 1972). LC_{50} values for nine saltwater fish species range from 0.2 to 4.2 µg/l. Saltwater invertebrates were slightly more sensitive, with LC_{50} values ranging from 0.14 to 10.0 µg/l (U.S. EPA, 1979a).

Concentrations as low as 8 µg/l elicited hyperactive locomotor responses in bluegill (Lepomis macrochirus) over 16 days old (Ellgaard, et al. 1977). The acute LD_{50} in adult summer frogs (Rana temooraria) was only 7.6 mg/kg. Though adipose tissues contained most of the DDT, the ovaries of females contained as much of the compound as did bones and spleen (Harri, et al. 1979).

B. Chronic Toxicity

Only one chronic freshwater fish value is available (Pimephales promelas), indicating that the chronic toxicity value is 0.74 µg/l (Jarvinen, et al., 1977). Freshwater invertebrate chronic toxicity data are not available. Concentration of DDT affecting three saltwater invertebrate species in chronic studies are similar in LC_{50} values (U.S. EPA, 1979a).

C. Plant Effects

Four species of freshwater algae (Calovella sp.) have evidenced a wide range of sensitivities, 0.3 to 800 µg/l (Sodergren, 1968). Wurster (1968) investigated the effects of DDT on four species of marine algae. The

data showed reduced rates of photosynthesis at 10 µg/l, indicating that algae are much less sensitive to DDT than are fish and invertebrates.

D. Residues

DDT is bioconcentrated to a very high degree in aquatic organisms. An average bioconcentration factor (BCF) of 640,000 has been calculated from 31 experimental measurements of bioconcentration done on 26 species of freshwater fish. Individual BCF's ranged from 490 to 2,236,666. In the field, BCF factors have been observed which are seven times higher than the average values derived from laboratory data. This discrepancy may be due to the many additional trophic levels involved and the possibly higher lipid content of the organisms in the field. In saltwater species, the BCF for DDT ranges from 800 to 76,300 times for fish and shellfish (U.S. EPA, 1979a). The lowest observed allowable maximum tissue concentration was 0.5 µg/kg for domestic animals in animal feed (U.S. FDA, 1977) and in the brown pelican (Pelecanus occidentalis) for eggshell thinning (Blus, et al. 1972, 1974).

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979c), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

The existing guidelines and standards for DDT are:

YEAR	AGENCY/ORG.	STANDARD	REMARKS
1971	WHO	0.005 mg/kg body weight	Maximum Acceptable Daily Intake in food
1976	U.S. EPA	0.001 µg/l	Ambient Water Quality Criteria

1977	Natl. Acad. Sci., Natl. Res. Counc.	-	In light of carcinogenic risk projection, suggested strict criteria for DDT and DDE in drinking water
1978	Occup. Safety Health Admin.	1 mg/m^2	Skin exposure
1978	U.S. EPA	0.41 µg/l 0.00023 µg/l	Final acute and chronic values for water quality criteria for protection of aquatic life (freshwater)

The U.S. EPA (1979a) is in the process of establishing ambient water quality criteria. Based on the potential carcinogenicity of DDT, current draft criteria are calculated on the estimate that 0.98 µg/man/day would result in an increased additional lifetime cancer risk of no more than 1/100,000. Since man and the rat appear to be less sensitive than mice, greater levels may be tolerable.

8. Aquatic

For DDT, the proposed draft criterion to protect freshwater aquatic life is 0.00023 µg/l as a 24-hour average; the concentration should not exceed 0.41 µg/l at any time. For saltwater aquatic species, the concentration is 0.0067 µg/l as a 24-hour average and should not exceed 0.021 µg/l at any time (U.S. EPA, 1979a).

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No. 61

Dibromochloromethane

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

DIBROMOCHLOROMETHANE

SUMMARY

Dibromochloromethane has been detected in drinking water in the United States. It is believed to be formed by the haloform reaction that may occur during water chlorination. Dibromochloromethane can be removed from drinking water via treatment with activated carbon. There is a potential for dibromochloromethane to accumulate in the aquatic evironment because of its resistance to degradation. Volatilization is likely to be an important means of environmental transport.

Very little toxicity information is available. Dibromochloromethane gave positive results in mutagenicity tests with Salmonella typhimurium TA100. It is currently under test by the National Cancer Institute.

I. INTRODUCTION

Dibromochloromethane ($CHBr_2Cl$, molecular weight 208.29) is a clear, colorless liquid. It is insoluble in water, but is soluble in a number of organic solvents. Its boiling point is 119-120°C and its density is 2.45 at 20°C (Weast, 1972). At 10.5°C, its vapor pressure is 15 torr (Dreisbach, 1952).

A review of the production range (includes importation) statistics for dibromochloromethane (CAS No. 124-48-1) which is listed in the initial TSCA Inventory (1979) has shown that

between 0 and 900 pounds of this chemical were produced/imported in 1977.*/

Dibromochloromethane is used as a chemical intermediate in the manufacture of fire extinguishing agents, aerosol propellants, refrigerants, and pesticides (Verschueren, 1977).

II. EXPOSURE

A. Environmental Fate

No information was found pertaining to the rate of oxidation of dibromochloromethane in either the aquatic or atmospheric environments. Dibromochloromethane is probably like other halogenated aliphatics in that it is not easily oxidized in aquatic systems because there are no functional groups which react strongly with HO radical. A maximum hydrolytic half-life of 274 years has been reported for dibromochloromethane at pH 7 and 25°C (Mabey and Mill, 1978).

The vapor pressure of dibromochloromethane, while lower than that for chloroform and other chloroalkanes, is, nonetheless, sufficient to ensure that volatilization will be an important means of environmental transport. The concentration of dibromochloromethane present in water supplies has been reported to

*/ This production range information does not include any production/importation data claimed as confidential by the person(s) reporting for the TSCA Inventory, nor does it include any information which would compromise Confidential Business Information. The data submitted for the TSCA Inventory, including production range information, are subject to the limitations contained in the Inventory Reporting Regulations (40 CFR 710).

decrease as a result of volatilization while flowing through open channels (Rook, 1974).

B. Bioaccumulation

The log of the octanol/water partition coefficient (log P) as calculated by the method of Hansch is 2.09 (Tute, 1971) indicating that dibromochloromethane is somewhat lipophilic. As a result, dibromochloromethane may exhibit a tendency to bioaccumulate in organisms. No experimental data were found to confirm this.

C. Environmental Occurrence

Dibromochloromethane has been detected in finished drinking water (Kleoper and Fairless, 1972; U.S. EPA, 1975), in drinking water supplies (U.S. EPA, 1975), and in wastewater effluents (Glaze and Henderson, 1975). Dibromochloromethane is hypothesized to be present in water supplies as a result of the haloform reaction which takes place during the chlorination of such water (Rook, 1974; U.S. EPA, 1975; Glaze and Henderson 1975).

III. HEALTH EFFECTS

A. Carcinogenicity

Dibromochloromethane is currently under test for carcinogenicity by the National Cancer Institute. No results are available.

B. Mutagenicity

Dibromochloromethane was found mutagenic in Salmonella typhimurium TA100 in the absence of metabolic activation (Simmon, 1977).

C. Other Toxicity

A long-term test conducted by administration of high doses of the chemical by gavage in mice showed a dose-dependent decrease in the activity of liver and spleen phagocytes (Munson et al., 1978).

The oral LD_{50} of dibromochloromethane in mice is 800 mg/kg and 1200 mg/kg for males and females respectively. Sedation and anesthesia occurred within 30 minutes of administration of the compound and lasted 4 hours. Necropsies were performed on animals that died. Hemorrhaging was observed in the adrenals, the kidneys were pale, and the liver appeared to have fatty infiltration (Bowman, 1978).

IV. AQUATIC EFFECTS

No information was found.

V. EXISTING GUIDELINES

The Maximum Contaminant Level (MCL) for total trihalomethanes (including dibromochloromethane) in drinking water has been set by the U.S. EPA at 0.10 mg/l (44 FR 68624). The concentration of dibromochloromethane produced by chlorination can be reduced by treatment of drinking water with powdered activated carbon (Rook, 1974). This is the technology that has been proposed by the EPA to meet this standard.

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No. 62

Di-n-butyl Phthalate

Health and Environmental Effects

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WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

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DI-n-BUTYL PHTHALATE

Summary

Teratogenic effects in rats have been reported in testing of di-n-butyl phthalate following i.p. administration, but not after oral administration at high doses (0.600 g/kg/day). Other reproductive effects in rats following i.p. administration include impaired implantation and parturition. Rats fed di-n-butyl phthalate or its monoester metabolite have developed testicular damage and atrophy.

Mutagenic or carcinogenic effects of di-n-butyl phthalate have not been reported.

One clinical study has indicated that workers exposed primarily, but not exclusively, to di-n-butyl phthalate showed a higher incidence of toxic polyneuritis.

The only toxicity data available for review demonstrate that di-n-butyl phthalate is acutely toxic to freshwater organisms at concentrations as low as 730 µg/l.

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DI-n-BUTYL PHTHALATE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Phthalate Esters (U.S. EPA, 1979a).

Di-n-Butyl phthalate (DBP) is a diester of the ortho form of benzene dicarboxylic acid. The compound has a molecular weight of 278.34, specific gravity of 1.0465, boiling point of 340°C and a solubility of 0.45 gms per 100 ml of water at 25°C (U.S. EPA, 1979a).

DBP is used as a plasticizer in polyvinyl acetate emulsions and as an insect repellent.

Current Production: 8.3×10^3 tons/year in 1977 (U.S. EPA, 1979a).

Phthalates have been detected in soil, air, and water samples, in animal and human tissues, and in certain vegetation. Evidence from *in vitro* studies indicates that certain bacterial flora may be capable of metabolizing DBP to the monoester form (Engelhardt, et al. 1975). For additional information regarding the phthalate esters in general, the reader is referred to the EPA/ECAO Hazard Profile on Phthalate Esters (U.S. EPA, 1979b).

II. EXPOSURE

Phthalate esters appear in all areas of the environment. Environmental release of phthalates may occur through leaching of the compound from plastics, volatilization of phthalate from plastics, or the incineration of plastic items. Sources of human exposure to phthalates include contaminated foods and fish, dermal application, and parenteral administration by use of plastic blood bags, tubings, and infusion devices (mainly DEHP release). Relevant factors in the migration of phthalate esters from packaging materials to food and beverages are: temperature, surface area contact, lipoidal nature of the food and length of contact (U.S. EPA, 1979a).

Monitoring studies have indicated that most water phthalate concentrations are in the ppm range, or 1-2 μg/liter (U.S. EPA, 1979a). Industrial air monitoring studies have measured air levels of phthalates from 1.7 to 66 mg/m^3 (Milkov, et al. 1973). Levels of DBP in foods have ranged from not detectable to 60 ppm (Tomita, et al. 1977). Cheese, milk, fish and shellfish present potential sources of high phthalate intake (U.S. EPA, 1979a). The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor for DBP to be 26 for the edible portions of fish and shellfish consumed by Americans. This estimate was based on the octanol/water partition coefficient.

III. PHARMACOKINETICS

A. Absorption

A human study in which subjects ate food containing DBP leached from plastic containers shows significantly higher levels of DBP found in the blood (Tomita, et al. 1977).

B. Distribution

Pertinent data could not be located in the available literature.

C. Metabolism

Monobutyl phthalate has been identified as a urinary metabolite in rabbits administered DBP (Ariyoshi, et al. 1976). This metabolite has also been detected in the urine of rats, hamsters, and guinea pigs, as well as other metabolites with side chain oxidation, and phthalic acid (Tanaka, et al. 1978).

D. Excretion

Pertinent data could not be located in the available literature.

IV. EFFECTS

A. Carcinogenicity

Pertinent data could not be located in the available literature.

B. Mutagenicity

Mutagenic effects of DBP were not observed in the Ames Salmonella assay (Rubin, et al. 1979) or in a yeast (Saccharomyces) assay system (Shahin and VonBorstel, 1977).

C. Teratogenicity

Teratogenic effects were not produced by DBP, (0.600 g/kg/day), following oral administration to pregnant rats (Nikonorow, et al. 1973) while Singh, et al. (1972) reported teratogenic effects of DBP following i.p. injection of pregnant rats.

D. Other Reproductive Effects

Intraperitoneal injection of DBP to pregnant rats showed that adverse effects prior to gestation day six were primarily on implantation, while after this day the effect was primarily on parturition (Peters and Cook 1973).

Testicular damage has been reported in rats fed DBP or its monoester metabolite (Carter, et al. 1977).

E. Chronic Toxicity

An increase in toxic polyneuritis has been reported by Milkov, et al. (1973) in workers exposed primarily to dibutyl phthalate. Lesser levels of exposure to dioctyl, diisooctyl, and benzylbutyl phthalates, and to tricresyl phosphate were also noted in these workers.

V. AQUATIC TOXICITY

A. Acute Toxicity

Acute toxicity for di-n-butyl phthalate ranged from a 96-hour static LC_{50} of 730 µg/l for the bluegill sunfish (Lepomis macrochirus) to 6,470 µg/l for the rainbow trout (Salmo gairdneri) (Mayer and Sanders, 1973). The freshwater scud (Gammarus pseudolimnaeus) was shown to provide a 48-hour static LC_{50} value of 2,100 ug/l di-n-butyl phthalate. Marine data were not available for review.

B. Chronic

Pertinent data could not be located in the available literature.

C. Plants

Pertinent data could not be located in the available literature.

D. Residues

Bioconcentration factors ranging from 400 to 1400 have been obtained for the aquatic invertebrates Daphnia magna and Gammarus pseudolimnaeus.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have gone through the process of review; therefore, there is a possibility that these criteria may be changed.

A. Human

Based on "no effect" levels observed in chronic feeding studies in rats or dogs, the U.S. EPA (1979a) has calculated an acceptable daily intake (ADI) level of 12.6 mg/day.

The recommended water quality criterion level for protection of human health is 5 mg/liter for DBP (U.S. EPA, 1979a).

B. Aquatic

The data base for toxic effects in both freshwater and marine environments was insufficient for the drafting of a water quality criterion to protect aquatic organisms.

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No. 63

Dibenzo(a,h)anthracene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated dibenzo(a,h)anthracene and has found sufficient evidence to indicate that this compound is carcinogenic.

DIBENZO(a,h)ANTHRACENE

Summary

Dibenzo(a,h)anthracene (DBA) is a member of the polycyclic aromatic hydrocarbon (PAH) class. DBA was the first pure chemical shown to produce tumors in animals. It is carcinogenic by skin application, by injection, and by oral administration to rodents. Since humans are not exposed to only DBA in the environment, it is not possible to attribute human cancers solely to exposure to DBA. Furthermore, it is not known how DBA may interact with other carcinogenic and non-carcinogenic PAH in human systems.

DIBENZO(a,h)ANTHRACENE

I. INTRODUCTION

This profile is based primarily on the Ambient Water Quality Criteria Document for Polynuclear Aromatic Hydrocarbons (U.S. EPA, 1979a) and the Multimedia Health Assessment Document for Polycyclic Organic Matter (U.S. EPA. 1979b).

Dibenzo(a,h)anthracene (DBA; $C_{22}H_{14}$) is one of the family of polycyclic aromatic hydrocarbons (PAH) formed as a result of incomplete combustion of organic material. Other than a reported melting point of 266-266.5°C (U.S. EPA. 1979b), its physical and chemical properties have not been well-characterized.

PAH, including DBA are ubiquitous in the environment, being found in ambient air, food, water, soils and sediment (U.S. EPA. 1979b). The PAH class contains a number of potent carcinogens (e.g., benzo(a)pyrene), moderately active carcinogens (e.g., benzo(b)fluoranthene), weak carcinogens (benz(a)anthracene), and cocarcinogens (e.g., fluoranthene), as well as numerous non-carcinogens (U.S. EPA. 1979b).

PAH which contain more than three rings (such as DBA) are relatively stable in the environment, and may be transported in air and water by adsorption to particulate matter. However, biodegradation and chemical treatment are effective in eliminating most PAH in the environment.

II. EXPOSURE

A. Water

Levels of DBA in water have not been reported. However, the concentration of six representative PAH (benzo(a)pyrene, fluor-

anthene, benzo(j)fluoranthene, benzo(k)fluoranthene, benzo(ghi)-perylene, indeno(1,2,3-cd-pyrene) in United States drinking water averaged 13.5 nanograms/liter (Basu and Sacena, 1977, 1978).

B. Food

Based on limited monitoring studies, DBA has been detected in various foods, such as, butter and smoked fish. Although, it is not possible to estimate the human dietary intake of DBA, it has been concluded (U.S. EPA. 1979b) that the daily dietary intake of all types of PAH is about 1.6 to 16 µg per day. The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor of DBA to be 24,000 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficient for DBA.

C. Inhalation

Levels of DBA have not been monitored in ambient air. However, it has been estimated that the average total PAH level in ambient air is about 10.9 nanograms/m^3 (U.S. EPA, 1979a). Thus the total daily intake of PAH by inhalation of ambient air may be about 207 nanograms, assuming that a human breathes 19 m^3 of air per day.

III. PHARMACOKINETICS

There are no data available concerning the pharmacokinetics of DBA, or other PAH, in humans. Nevertheless, it is possible to make limited assumptions based on the results of animal research conducted with several PAH, particularly benzo(a)pyrene.

A. Absorption

The absorption of DBA in humans or other animals has not been thoroughly studied. However, it is known (U.S. EPA, 1979a) that, as a class, PAH are well-absorbed across the respiratory and

gastrointestinal epithelia. The high lipid solubility of compounds in the PAH class supports this observation.

B. Distribution

Only limited work on distribution of DBA in mammals has been performed (Heidelberger and Weiss, 1959). However, it is known (U.S. EPA, 1979a) that other PAH become localized in a wide variety of body tissues following their absorption in experimental rodents. Relative to other tissues, PAH tend to localize in body fat and fatty tissues (e.g., breast).

C. Metabolism

The mammalian metabolism of DBA has been well-characterized (Sims, 1976). DBA, like other PAH, is metabolized by the microsomal mixed function oxidase enzyme system in mammals (U.S. EPA. 1979b). Metabolic attack on one or more of the aromatic rings leads to the formation of phenols, and isomeric dihydrodiols by the intermediate formation of reactive epoxides. Dihydrodiols are further metabolized by microsomal mixed function oxidases to yield diol epoxides, compounds which are known to be ultimate carcinogens for certain PAH. Removal of activated intermediates by conjugation with glutathione or glucuronic acid, or by further metabolism to tetrahydrotetrols, is a key step in protecting the organism from toxic interaction with cell macromolecules.

D. Excretion

There is no direct information available concerning the excretion of PAH in man. The excretion of DBA however, by mice was studied by Heidelberger and Weiss (1959). The excretion of DBA was

rapid and occurred mainly via the feces. Elimination in the bile accounts for a significant percentage of all administered PAH (U.S. EPA, 1979a). It is unlikely that PAH will accumulate in the body with chronic low-level exposures.

IV. EFFECTS

A. Carcinogenicity

DBA was the first pure chemical ever shown to produce tumors in animals. DBA has considerable carcinogenic potency when applied to the skin of mice (Iball, 1939; U.S. EPA. 1979b), injected subcutaneously in mice (U.S. EPA. 1979b), injected into newborn mice (Beuning, et al. 1979), injected into Strain A mice (Shimkin and Stoner, 1975) or administered orally to mice (Snell and Stewart, 1962).

B. Mutagenicity

DBA is a mutagenic in the Ames Salmonella assay (Andrews, et al. 1978; Wood, et al. 1978) in cultured hamster cells (Huberman and Sacks, 1974), and is positive in the in vivo sister-chromatid exchange assay in Chinese hamsters (Roszinsky-Kocher, et al. 1979).

C. Teratogenicity

There are no data available concerning the possible teratogenicity of DBA in man. Other related PAH apparently are not significantly teratogenic in mammals (U.S. EPA, 1979a).

D. Other Reprodutive Effects

Pertinent information could not be located in the available literature.

E. Chronic Toxicity

As long ago as 1937, investigators knew that carcinogenic PAH, including DBA, could inhibit growth in rats and mice (Haddow, et al. 1937). In early studies, DBA was administered to mice in weekly subcutaneous injections for 40 weeks, which produced increased reticulum (stem) cells, dilation of lymph sinuses, and decreased spleen weights in comparison to controls (Hoch-Ligeti, 1941).

A more detailed study of subchronic effects of DBA on lymph nodes of male rats was reported in 1944 (Lasnitzki and Woodhouse, 1944). Subcutaneous injections given five times weekly for several weeks caused normal lymph nodes to undergo hemolymphatic changes.

V. AQUATIC TOXICITY

Pertinent information could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have yet gone through the process of public review; therefore, there is a possibility that these criteria may be changed.

A. Human

There are no established exposure criteria for DBA. However, PAH as a class are regulated by several authorities. The World Health Organization recommends that the concentration of PAH in drinking water (measured as the total of fluoranthene, benzo-(g,h,i)perylene, benzo(b)fluoranthene, benzo(k)fluoranthene, in

deno(1,2,3-cd)pyrene, and benzo(a)pyrene) not exceed 0.2 µg/l. Occupational exposure criteria have been established for coke oven emissions, coal tar products, and coal tar pitch volatiles, all of which contain large amounts of PAH including DBA (U.S. EPA, 1979a).

The U.S. EPA (1979a) draft recommended criteria for PAH in water are based upon the extrapolation of animal carcinogenicity data for benzo(a)pyrene and DBA. Levels for each compound are derived which will result in specified risk levels of human cancer as shown in the table below.

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria ng/l			
	0	10^{-7}	10^{-6}	10^{-5}
BaP				
2 liters of drinking water and consumption of 18.7 grams fish and shellfish	0	0.097	0.97	9.7
Consumption of fish and shellfish only		0.44	4.45	44.46
DBA				
2 liters of drinking water and consumption of 18.7 grams fish and shellfish	0	0.43	4.3	43
Consumption of fish and shellfish only.		1.96	19.6	196

B. Aquatic

The criterion for freshwater and marine life have not been derived (U.S. EPA, 1979a).

DIBENZO(a,h)ANTHRACENE

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No. 64

1,2-Dichlorbenzene

Health and Environmental Effects

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APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

1,2-DICHLOROBENZENE

SUMMARY

1,2-Dichlorobenzene is a lipophilic compound which upon absorption into the body, deposits in the fatty tissues. This compound is detoxified by the liver microsomal enzymes. On chronic exposure to 0.1 mg 1,2-dichlorobenzene/kg, rats developed anemia, liver damage, and central nervous system depression. There have not been studies available to determine the carcinogenic or teratogenic potential of 1,2-dichlorobenzene. 1,2-Dichlorobenzene was mutagenic when tested with the mold Aspergillis nidulans and negative when tested with the bacteria Salmonella typhimurium in the Ames assay.

The toxicity of 1,2-dichlorobenzene appears to be similar for freshwater and marine organisms with reported LC_{50} values ranging between 1,970 and 27,000 µg/l.

1,2-DICHLOROBENZENE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Dichlorobenzenes (U.S. EPA, 1979a).

1,2-Dichlorobenzene (1,2-DCB or ODCB; $C_6H_4Cl_2$; molecular weight 147.01) is a liquid at normal environmental temperatures. 1,2-Dichlorobenzene has a melting point of -17.6°C, a boiling point of 179°C, a density of 1.30 g/ml at 20°C, a water solubility of 145,000 µg/l at 25°C, and a vapor pressure of 1 mm Hg at 20°C (Weast, 1975). The major uses of 1,2-dichlorobenzene are as a process solvent in the manufacturing of toluene diisocyanate and as an intermediate in the synthesis of dyestuffs, herbicides, and degreasers (West and Ware, 1977).

II. EXPOSURE

A. Water

1,2-Dichlorobenzene has been detected in rivers, groundwater, municipal and industrial discharges, and drinking water. 1,2-Dichlorobenzene has been reported entering water systems at average levels of 2 mg/l as a result of its use by industrial wastewater treatment plants for odor control (Ware and West, 1977). In 4 out of 110 drinking waters, 1,2-dichlorobenzene was detected at an average concentration of 2.5 µg/l (U.S. EPA, 1979a). Also, 1,2-dichlorobenzene may be formed during chlorination of water containing organic precursor material (Glaze, et al. 1976).

B. Food

There are not enough data to state quantitatively the degree of 1,2-dichlorobenzene exposure through total diet (U.S. EPA, 1979a). The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor of 1,2-dichlorobenzene to be 200 for the edible portion of aquatic organisms consumed by Americans. This estimate is based on measured steady-state bioconcentration studies in bluegill.

C. Inhalation

1,2-Dichlorobenzene has been detected on airborne particulate matter in California at concentrations between 8 and 53 ng/m^2 (Ware and West, 1977). There is no other available information on the concentration of this compound in ambient air (U.S. EPA, 1979a).

III. PHARMACOKINETICS

A. Absorption

There is little information provided in U.S. EPA (1979a) on the absorption specifically of 1,2-dichlorobenzene. General information on the absorption of dichlorobenzenes can be found in the Hazard Profile for Dichlorobenzenes (U.S. EPA, 1979b). Reidel (1941) has reported absorption of 1,2-dichlorobenzene through the skin of rats in lethal amounts after five dermal applications under severe test conditions (painting twice daily directly on a 10 cm^2 area of abdominal skin). Also, 1,2-dichlorobenzene fed to rats at less than 0.4 to 2 mg/kg/day was absorbed and accu-

mulated in various tissues indicating significant absorption by the gastrointestinal tract even at low levels of exposure (Jacobs, et al. 1974a,b).

B. Distribution

After feeding rats low levels of 1,2-dichlorobenzene, in combination with other trace pollutants found in the Rhine River, tissue accumulation was greater in fat than in the liver, kidney, heart, and blood (Jacobs, et al. 1974a).

C. Metabolism

The metabolism of 1,2-dichlorobenzene was studied by Azouz, et al. (1955) in rabbits. 1,2-Dichlorobenzene was mainly metabolized by oxidation to 3,4-dichlorophenol followed by the formation of conjugates with glucuronic and sulfuric acids. Minor oxidative metabolites and their conjugates were also detected.

D. Excretion

Excretion of the metabolic products of 1,2-dichlorobenzene in the rabbit was mainly through the urine (Azouz, et al. 1955).

IV. EFFECTS

A. Carcinogenicity

Specific positive evidence of the carcinogenicity of DCB's is lacking. However, a sufficient collection of varied data exist to suggest prudent regard of DCB as a potential carcinogen (U.S. EPA, 1979a).

B. Mutagenicity

Treatment of the soil mold Aspergillus nidulans for one hour in an ether solution of 1,2-dichlorobenzene increased the frequency of back-mutations (Prasad, 1970). In the Ames assay, 1,2-dichlorobenzene did not increase the mutational rate of the histidine-requiring strains of Salmonella typhimurium (Andersen, et al. 1972).

C. Teratogenicity

Studies of the teratogenicity of 1,2-dichlorobenzene could not be located in the available literature.

D. Other Reproductive Effects

Information is not available.

E. Chronic Toxicity

In an inhalation study, Hollingsworth, et al. (1958) exposed groups of 20 rats, 8 guinea pigs, 4 rabbits, and 2 monkeys to the vapor of 1,2-dichlorobenzene seven hours per day, five days per week for six to seven months at an average concentration of 560 mg/m^3. No adverse effects were noted in behavior, growth, organ weights, hematology, or upon gross and microscopic examination of tissues. In a nine month chronic toxicity study, Varshavskaya (1967) gave rats 1,2-dichlorobenzene at daily doses of 0.001, 0.01, and 0.1 mg/kg. The toxicological observations in the highest dose group were anemia and other blood changes, liver damage, and central nervous system depression. The highest no-observable-adverse-effect level for 1,2-dichlorobenzene by Varshavskaya (1967) was 0.001 mg/kg/day, whereas the compar-

able level in the rat study by Hollingsworth, et al. (1958) was 18.8 mg/kg/day.

F. Other Relevant Information

1,2-Dichlorobenzene can induce microsomal drug metabolizing enzymes (Ware and West, 1977).

V. AQUATIC TOXICITY

A. Acute Toxicity

For freshwater fish, two 96-hour static bioassays have produced LC_{50} values of 5,590 and 27,000 µg/l for the bluegill (Lepomis macrochirus) (U.S. EPA, 1978; Dawson, et al. 1977). A single 96-hour static assay for the freshwater invertebrate Daphnia magna provided an LC_{50} value of 2,440 µg/l. In marine fish, LC_{50} values reported were 7,300 µg/l for the tidewater silverside (Menidia beryllina) and 9,660 µg/l for the sheepshead minnow (Cyprinodon variegatus) (U.S. EPA, 1978). An adjusted LC_{50} value of 1,970 µg/l was obtained for the marine invertebrate (Mysidopsis bahia).

B. Chronic

The only freshwater organisms tested were embryo-larval stages of the fathead minnow (Pimephales promelas), which produced a chronic value of 1,000 µg/l for 1,2-dichlorobenzene. No chronic data for marine organisms were available for evaluation.

C. Plants

The freshwater algae Selenastrum capricornutum has been tested for the effects of 1,2-dichlorobenzene on

chlorophyll a and cell numbers. The EC_{50} values were 91,600 and 98,000 µg/l, respectively, while comparable values of 44,200 to 44,100 µg/l were reported for the marine algae Skeletonema costatum (U.S. EPA, 1978).

D. Residues

A bioconcentration of 89 was obtained for the bluegill.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The Occupational Safety and Health Administration (OSHA, 1976), and the American Conference of Governmental Industrial Hygienists (ACGIH, 1977) threshold limit value is 300 mg/m^3 for 1,2-dichlorobenzene. The U.S. EPA (1979a) draft water quality criterion for total dichlorobenzene (all three isomers) is 160 µg/l.

B. Aquatic

Criteria have been drafted for freshwater organisms as 44 µg/l for the 24-hour average concentration, not to exceed 99 µg/l. The marine draft criterion is 15 µg/l not to exceed 34 µg/l (U.S. EPA, 1979a).

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No. 65

1,3-Dichlorobenzene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

1,3-DICHLOROBENZENE

Summary

1,3-Dichlorobenzene is not used commercially and is produced only as a by-product in the manufacture of chlorinated benzenes. This compound is metabolized by the liver mixed function oxidase system. Little is known of the toxicological, teratogenic, or carcinogenic properties of this compound. 1,3-Dichlorobenzene has been shown to be mutagenic to the soil mold Aspergillus nidulans. Since 1,3-dichlorobenzene may be a contaminant of the other dichlorobenzenes, some of the toxicologic properties ascribed to these isomers may be due to the 1,3-isomer.

For freshwater and marine fish and invertebrates, acute toxicity values ranged from 2,414 to 4,248 µg/l, but the freshwater invertebrate, Daphnia magna, was more resistant to 1,3-dichlorobenzene with an acute value of 23,800 µg/l.

1,3-DICHLOROBENZENE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Dichlorobenzenes (U.S. EPA, 1979a).

1,3-Dichlorobenzene (1,3-DCB; MDCB; $C_6H_4Cl_2$; molecular weight 147.01) is a liquid at normal environmental temperatures, has a melting point of -24.2°C, a boiling point of 172°C, a density of 1.29 g/ml at 20°C, a water solubility of 123,000 µg/l at 25°C, and a vapor pressure of 5 mm Hg at 39°C (Weast, 1975). 1,3-Dichlorobenzene may occur as a contaminant of 1,2- or 1,4-dichlorobenzene formulations (U.S. EPA, 1979a).

II. EXPOSURE

A. Water

1,3-Dichlorobenzene has been detected or quantified in groundwater, raw water, and drinking water. In two of 110 drinking water samples, 1,3-dichlorobenzene was detected at an average concentration of 0.1 µg/l (U.S. EPA, 1979a). Also, 1,3-dichlorobenzene may be formed during chlorination of raw and waste water containing organic precursor material (Glaze, et al. 1976).

B. Food

The data are insufficient to state quantitatively the degree of 1,3-dichlorobenzene exposure through total diet (U.S. EPA, 1979a). 1,3-Dichlorobenzene is reported to be among several metabolites of gamma-pentachloro-1-cyclohexane found in corn and pea seedlings (Mostafa and Moza, 1973). The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor to be 150 for 1,3-dichlorobenzene for the edible portions of fish and shellfish consumed by Americans. This estimate is based on measured steady- state bioconcentration studies in bluegill.

C. Inhalation

Pertinent data could not be located in the available literature.

III. PHARMACOKINETICS

A. Absorption

Specific information on the absorption of 1,3-dichlorobenzene was not found in the available literature. General information on the absorption of the dichlorobenzenes can be found in the Hazard Profile for Dichlorobenzenes (U.S. EPA, 1979b).

B. Distribution

Specific information on the distribution of 1,3-dichlorobenzene was not found in the available literature. Reference may be made to the Hazard Profile for Dichlorobenzene (U.S. EPA, 1979b) and the 1,2-isomer (U.S. EPA, 1979c).

C. Metabolism

The metabolism of 1,3-dichlorobenzene in rabbits was studied by Parke and Williams (1955). 1,3-Dichlorobenzene was mainly metabolized by oxidation to 2,4-dichlorophenol followed by the formation of the glucuronides and ethereal sulfates. Minor oxidative metabolites and their conjugates were also detected.

D. Excretion

Excretion of the metabolic products of 1,3-dichlorobenzene in the rabbit is mainly through the urine with excretion being essentially complete within five days (Parke and Williams, 1955).

IV. EFFECTS

A. Carcinogenicity

Reports of specific carcinogenicity tests of 1,3-dichlorobenzene in animals or of pertinent epidemiologic studies in humans were not found in the available literature (U.S. EPA, 1979a).

B. Mutagenicity

Treatment of the soil mold Aspergillus nidulans for one hour in an ether solution of 1,3-dichlorobenzene increased the frequency of back mutations (Prasad, 1970).

C. Teratogenicity and Other Reproductive Effects

Studies of the teratogenicity and other reproductive effects of 1,3-dichlorobenzene were not found in the available literature.

D. Chronic Toxicity

Specific information on the chronic toxicity of 1,3-dichlorobenzene was not found in the available literature. However, 1,3-dichlorobenzene may have been a contaminant of the 1,2- and 1,4-dichlorobenzenes used in toxicological studies. For further information on the general toxicologic properties of the dichlorobenzenes, refer to the Hazard Profile for Dichlorobenzenes (U.S. EPA, 1979b).

E. Other Relevant Information

1,3-Dichlorobenzene can induce microsomal drug metabolizing enzymes. Changes in the levels of microsomal enzymes can affect the metabolism and biological activity of a wide variety of xenobiotics (Ware and West, 1977).

V. AQUATIC TOXICITY

A. Acute Toxicity

For the bluegill (Lepomis macrochirus), a 96-hour static LC_{50} of 5,020 µg/l has been obtained. The freshwater invertebrate, Daphnia magna, has a much higher LC_{50} of 28,100 µg/l for a 48-hour static assay. For the sheepshead minnow, an acute LC_{50} of 7,770 µg/l has been obtained. A value of 2,850 µg/l has been obtained for the marine mysid shrimp (Mysidopsis bahia) (U.S. EPA, 1978).

B. Chronic

Chronic studies with either freshwater or marine species are not available.

C. Plant Effects

The freshwater alga Selenastrum capricornutum was tested for the effects of 1,3-dichlorobenzene on chlorophyll a and cell numbers. The EC_{50} values ranged from 149,000-179,000 µg/l. For the marine alga Skeletonema costatum, the EC_{50} values for cell number and chlorphyll a ranged from 49,600-52,800 µg/l (U.S. EPA, 1979a).

D. Residues

A bioconcentration factor of 66 was obtained for the bluegill (U.S. EPA, 1979a).

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

There are no existing standards for 1,3-dichlorobenzene. The U.S. EPA (1979a) draft water quality criterion for total dichlorobenzene (all three isomers) is 160 µg/l.

B. Aquatic

A criterion for the protection of freshwater organisms has been drafted as 310 µg/l for a 24-hour average concentration not to exceed 700 µg/l. For marine life, the criterion has been proposed as 22 µg/l for 24-hour average not to exceed 49 µg/l.

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No. 66

1,4-Dichlorobenzene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

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1,4-DICHLOROBENZENE

SUMMARY

1,4-Dichlorobenzene is a lipophilic compound which, upon absorption into the body, deposits in the fatty tissues. This compound is detoxified by the liver microsomal enzymes. Chronic intoxication produces increased liver and kidney weights and abnormal liver pathology. Studies to determine the carcinogenic or teratogenic potential of 1,4-dichlorobenzene could not be located in the available literature. 1,4-Dichlorobenzene produces chromosomal aberrations in root tips and has been shown to increase the mutation rate in the mold Aspergillus nidulans.

Acute values for freshwater and marine organisms ranged from 1,990 to 11,000 µg/l for 1,4-dichlorobenzene. Marine in vertebrates were most sensitive and freshwater invertebrates were most resistant to the effects of 1,4-dichlorobenzene.

1,4-DICHLOROBENZENE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Dichlorobenzene (U.S. EPA, 1979a).

1,4-Dichlorobenzene ($C_6H_4Cl_2$; molecular weight 147.01) is a solid at normal environmental temperatures. 1,4-Dichlorobenzene has a melting point of 53.0°C, a boiling point of 174°C, a density of 1.25 g/ml at 20°C, a water solubility of 80,000 µg/l at 25°C, and a vapor pressure of 0.4 mm Hg at 25°C (Weast, et al. 1975). The primary use of 1,4-dichlorobenzene is as an air deodorant and insecticide. This compound is produced almost entirely as a byproduct during the manufacture of monochlorobenzene (Ware and West, 1977).

For a more general discussion of dichlorobenzene, the reader is referred to the Hazard Profile for Dichlorobenzene (U.S. EPA, 1979b).

II. EXPOSURE

A. Water

1,4-Dichlorobenzene has been detected or quantified in rivers, groundwater, municipal and industrial discharge, and drinking water. 1,4-Dichlorobenzene enters wastewater systems because of its use in toilet blocks (Ware and West, 1977). 1,4-Dichlorobenzene may also be formed during chlorination of raw and waste water containing organic percursor material (Glaze, et al. 1976). In 20 of 113 drinking water samples, 1,4-dichlorobenzene was detected at an average concentration of 0.14 µg/l (U.S. EPA, 1979a).

B. Food

There are not enough data available to quantitatively state the degree of 1,4-dichlorobenzene exposure through total diet (U.S. EPA, 1979a). Schmidt (1971) reported the tainting of pork as a result of the use of an odor control agent containing 1,4-dichlorobenzene in pig stalls. Also, Morita, et al. (1975) reported 0.05 mg/kg 1,4-dichlorobenzene in fish from Japanese coastal waters. The U.S EPA (1979a) has estimated the weighted bioconcentration factor of 1,4-dichlorobenzene to be 140 for the edible portion of fish and shellfish consumed by Americans. This estimate is based on measured steady-state bioconcentration studies in bluegills.

C. Inhalation

Morita and Ohi (1975) measured 1,4-dichlorobenzene in the vapor phase, in and around Tokyo, by use of a cold solvent trap. Urban levels were found to range from 2.7 to 4.2 $\mu g/m^3$, while suburban levels were lower, ranging from 1.5 to 2.4 $\mu g/m^3$; indoor levels were considerably higher, ranging 0.105 to 1.7 mg/m^3. No other information was found regarding the concentration of this compound in ambient air (U.S. EPA, 1979a).

III. PHARMAKINETICS

A. Absorption

In humans, toxic effects following accidentally or deliberately ingested 1,4-dichlorobenzene clearly indicate significant absorption by the gastrointestinal route (Campbell and Davidson, 1970; Frank and Cohen, 1961; Hallowell,

1959). Also, Azouz, et al. (1955) detected no 1,4-dichlorobenzene in the feces of rabbits dosed intragastrically with the compound in oil. This suggests virtually complete absorption under these conditions.

B. Distribution

The studies of Morita and Ohi (1975) and Morita, et al. (1975) have shown 1,4-dichlorobenzene in adipose tissue (mean about 2 mg/kg) and blood (about 0.01 mg/l) of humans exposed to ambient pollution levels in the Tokyo area.

C. Metabolism

The metabolism of 1,4-dichlorobenzene in rabbits was studied by Azouz, et al. (1955). 1,4-Dichlorobenzene was primarily metabolized by oxidation to 2,5-dichlorophenol, followed by the formation of the glucuronides and ethereal sulfates. Minor oxidative metabolites and their conjugates were also detected. Pagnatto and Walkley (1966) indicated that 2,5-dichlorophenol was also the principal metabolite of 1,4- dichlorobenzene in humans.

D. Excretion

Excretion of the metabolic products of 1,4-dichlorobenzene in the rabbit occurs mainly through the urine (Azouz, et al. 1955), with no mention made of fecal excretion.

IV. EFFECTS

A. Carcinogenicity

No reports of specific carcinogenicity tests of 1,4-dichlorobenzene in animals or of pertinent epidemiologic studies in humans were available. A few inconclusive experi-

ments which indicate further investigation of the carcinogenic potential of 1,4-dichlorobenzene is warranted are reviewed in U.S EPA (1979a).

B. Mutagenicity

Various mitotic anomalies were observed in cells and somatic chromosomes of 1,4-dichlorobenzene treated root tips (Carey and McDonough, 1943; Sharma and Sarkar, 1957; Srivastava, 1966). Treatment of Aspergillus nidulans (a soil mold organism) for one hour in an ether solution of 1,4-dichlorobenzene increased the frequency of back-mutations (Prasad, 1970).

C. Teratogenicity and Other Reproductive Effects

Pertinent data could not be located in the available literature.

D. Chronic Toxicity

Effects observed in rats and guinea pigs exposed to a concentration of 2,050 mg/m^3 1,4-dichlorobenzene for six months included: growth depression (guinea pigs); increased liver and kidney weights (rats); abnormal liver pathology (cloudy swelling, fatty degeneration, focal necrosis, cirrhosis) (Hollingsworth, et al. 1956). In animals exposed to 4,800 mg/m^3 1,4-dichlorobenzene, up to 25 percent deaths were noted; and in survivors, symptoms were noted that were similar to those observed at the lower dose. Similar pathology was also observed in female rats, who received 376 mg/kg dose of 1,4-dichlorobenzene by stomach tube 5 days a week for a total of 138 doses.

E. Other Relevant Information

1,4-Dichlorobenzene can induce microsomal drug-metabolizing enzymes. Changes in the levels of microsomal enzymes can affect the metabolism and biological activity of a wide variety of xenobiotics (Ware and West, 1977).

V. AQUATIC TOXICITY

A. Acute Toxicity

Acute 96-hour LC_{50} values for all aquatic species tested were relatively similar. For the freshwater fish, the bluegill (Lepomis macrochirus), a LC_{50} of 4,280 µg/l was obtained, while the freshwater invertebrate Daphnia magna was more resistant, with a LC_{50} value of 11,000. An LC_{50} value of 7,400 µg/l was obtained for the marine fish, the sheepshead minnow (Cyprinodon variegatus); and the myrid shrimp (Mysidopsis bahia) had an LC_{50} value of 1,990 µg/l (U.S. EPA, 1978).

B. Chronic

Pertinent data could not be located in the available literature.

C. Plants

The freshwater alga, Selenastrum capricornutum, when tested for the effects of 1,4-dichlorobenzene on chlorophyll a and cell numbers, was shown to have had a range of effective concentration of 96,700 to 98,100 µg/l, while the marine alga Skeletonema costatum was more sensitive, with an effective concentration range of 54,800 to 59,100 µg/l.

D. Residues

A bioconcentration factor of 60 was obtained for the freshwater bluegill.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The Occupational Safety and Health Administration Standard (OSHA, 1976), and the American Conference of Governmental Industrial Hygienists (ACGIH, 1977) threshold limit value are 450 mg/m^3 for 1,4-dichlorobenzene. The acceptable daily intake (ADI) of 1,4-dichlorobenzene is 0.94 mg/day (Natl. Acad. Sci., 1977). The U.S. EPA (1979a) draft water quality criterion for total dichlorobenzene (all three isomers) is 0.16 mg/l.

B. Aquatic

A criterion for the protection of freshwater aquatic life has been drafted as a 190 µg/l 24-hour average concentration, not to exceed 440 µg/l at any time. For the protection of marine life, the criterion is 15 µg/l as a 24-hour average, not to exceed 34 µg/l at any time.

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No. 67

Dichlorobenzenes

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DICHLOROBENZENES

Summary

Dichlorobenzenes are lipophilic compounds which, upon absorption into the body, deposit in the fatty tissues. These compounds are metabolized by the liver microsomal enzyme system to water soluble compounds. Chronic exposure to any of the three isomers produces effects on the liver, blood, central nervous system and respiratory tract. Studies to determine the carcinogenic or teratogenic potential of the dichlorobenzenes were not located in the available literature. In one study these compounds have increased the mutational rate of soil mold.

The position of the chlorine atoms on the benzene ring appears to have little significant effect on the toxicity of the 1,2-, 1,3-, or 1,4-dichlorobenzene isomers to fish and invertebrates, except for the apparent resistance of the freshwater invertebrate Daphnia magna to 1,3-chlorobenzene. Marine fish tend to be slightly more resistant than freshwater fish, although the inverse is true for freshwater and marine invertebrates.

DICHLOROBENZENES

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Dichlorobenzenes (U.S. EPA, 1979).

The dichlorobenzenes ($C_6H_4Cl_2$; molecular weight 147.01) are a class of halogenated aromatic compounds represented by three structurally similar isomers: 1,2-dichloro-, 1,3-dichloro-, and 1,4-dichlorobenzenes (Weast, et al. 1975). 1,2-Dichloro- and 1,3-dichlorobenzene are liquids at normal environmental temperatures while 1,4-dichlorobenzene is a solid. All the dichlorobenzenes boil at approximately 175°C and have a density close to 1.28 g/ml. The solubilities in water of the 1,2-, 1,3-, and 1,,4-dichlorobenzene isomers at 25°C are 145,000 µg/l, 123,000 µg/l, and 80,000 µg/l, respectively (Jacobs, 1957). The vapor pressure of 1,2-dichlorobenzene at 20°C is 1 mm Hg; the vapor pressure of 1,3-dichlorobenzene at 39°C is 3 mm Hg; and the vapor pressure of 1,4-dichlorobenzene at 25°C is 0.4 mm Hg (Jordan, 1954; Kirk and Othmer, 1963).

The major uses of 1,2-dichlorobenzene are as a process solvent in the manufacturing of toluene diisocyanate and as an intermediate in the synthesis of dyestuffs, herbicides, and degreasers. 1,4-Dichlorobenzene is used as an air deodorant and an insecticide. 1,3-Dichlorobenzene is found as a contaminant of the other two isomers. The combined annual production of 1,2-, and 1,4-dichlorobenzene in the United States approaches 50,000 metric tons (Ware and West, 1977).

II. EXPOSURE

A. Water

Dichlorobenzenes have been detected or quantified in rivers, ground water, municipal and industrial discharges, and drinking water. Dichlorobenzenes enter the water systems from the use of 1,2-dichlorobenzene as a deodorant in industrial wastewater treatment and from the use of 1,4-dichlorobenzene toilet blocks (Ware and West, 1977). Chlorinated benzenes may also be formed during chlorination of raw and wastewater containing organic precursor material (Glaze, et al. 1976). In two case studies the concentration of dichlorobenzene in finished water was higher than in the raw water supply (Gaffney, 1976).

B. Food

There are not enough data to state quantitatively the degree of dichlorobenzene exposure through total diet. Tainting of pork has been reported due to the use of an odor control product containing 1,4-dichlorobenzene in pig stalls (Schmidt, 1971). Also, low levels of contamination of plant products have been noted from the metabolism of lindane and gamma-pentachlor-1-cyclohexane (Balba and Saha, 1974; Mostafa and Moza, 1973). Morita, et al. (1975) reported detectable levels of 1,4-dichlorobenzene in fish of the Japanese coastal waters; the concentration was 0.05 mg/kg. The U.S. EPA (1979) has estimated the weighted average bioconcentration factors for the edible portion of fish and shellfish consumed by Americans for 1,2-dichloro-, 1,3-dichloro-, and 1,4-dichlorobenzene to be 200, 150, and 140, respectively. These estimates are based on measured steady-state bioconcentration studies in bluegills.

C. Inhalation

1,2-Dichlorobenzene has been detected in airborne particulate matter in California at concentrations between 8 and 53 ng/m^2 (Ware and West, 1977). Morita and Ohi (1975) measured 1,4-dichlorobenzene in the vapor phase, by the use of a cold solvent trap, in and around Tokyo. Urban levels were 2.7 to 4.2 $\mu g/m^3$; suburban levels were lower at 1.5 to 2.4 $\mu g/m^3$; however, indoor levels were considerably higher at 0.105 to 1.7 mg/m^3.

III. PHARMACOKINETICS

A. Absorption

The dichlorobenzenes may be absorbed through the lungs, gastrointestinal tract, and intact skin (Ware and West, 1977). There is no data on the quantitative efficiency of absorption of dichlorobenzenes; however, as indicated from the appearance of metabolites in the urine, respiratory absorption during inhalation exposure is rapid (Pagnatto and Walkley, 1966). In humans, toxic effects following accidentally or deliberately ingested 1,4-dichlorobenzene clearly indicate significant absorption by the gastrointestinal route (Campbell and Davidson, 1970; Frank and Cohen, 1961; Hallowell, 1959). Also, 1,2-dichlorobenzene fed to rats at less than 0.4 to 2 mg/kg/day was absorbed and accumulated in various tissues, indicating significant absorption by the gastrointestinal tract even at low levels of exposure by ingestion (Jacobs, et al. 1974a,b).

B. Distribution

After feeding rats low levels of 1,2-dichlorobenzene in combination with other trace pollutants found in the Rhine River, tissue accumulation was greater in fat than in the liver, kidney, heart, and blood (Jacobs, et al. 1974a). Studies of Morita and Ohi (1975) and Morita, et al. (1975) have

shown 1,4-dichlorobenzene in adipose tissue (mean about 2 mg/kg) and blood (about 0.01 mg/l) of humans exposed to ambient pollution levels in the Tokyo area.

C. Metabolism

Metabolism of the 1,2- and 1,4-dichlorobenzenes was studied by Azouz, et al. (1955), and 1,3-dichlorobenzene was studied by Parke and Williams (1955) in rabbits. These compounds are mainly metabolized by oxidation to 3,4-dichlorophenol, 2,5-dichlorophenol, and 2,4-dichlorophenol respectively, which are subsequently conjugated. Other oxidation products are formed to a lesser extent, followed again by conjugation. Pagnatto and Walkley (1966) indicated that 2,5-dichlorophenol was also the principal metabolite of 1,4-dichlorobenzene in humans.

D. Excretion

In studies of rabbits, Azouz, et al. (1955) and Parke and Williams (1955) reported the excretion of metabolic products of the dichlorobenzenes in the urine.

IV. EFFECTS

A. Carcinogenicity

No reports of carcinogenicity testing of specific dichlorobenzenes could be located in the available literature. Inconclusive experiments reviewed in U.S. EPA (1979) indicate that further investigation of the carcinogenic potential of the dichlorobenzenes is warranted.

B. Mutagenicity

Various mitotic anomalies were observed in cells and somatic chromosomes of 1,4-dichlorobenzene-treated root tips (Srivastava, 1966; Sharma and Sarkar, 1957; Carey and McDonough, 1943). Treatment of Aspergillus nidulans (a soil mold organism) for one hour in an ether

solution of any of the three isomers of dichlorobenzene increased the frequency of back-mutations (Prasad, 1970). In the Ames assay, 1,2-dichlorobenzene did not increase the mutational rate of the histidine-requiring strains of Salmonella typhimurium (Andersen, et al. 1972).

C. Teratogenicity and Other Reproductive Effects

Pertinent data could not be located in the available literature.

Campbell and Davidson (1970) reported the history of a woman who was eating p-DCB during her pregnancy, and which had no apparent effect on the offspring.

D. Chronic Toxicity

In humans, chronic occupational exposure by inhalation has occurred mainly from 1,4-dichlorobenzene and to a lesser extent 1,2-dichlorobenzene. Toxicity has involved the following organs and tissues: liver, blood (or reticuloendothelial system, including bone marrow and/or immune components), central nervous system, respiratory tract, and integument (U.S. EPA, 1979). In an inhalation study, Hollingsworth, et al. (1958) exposed groups of 20 rats, eight guinea pigs, four rabbits, and two monkeys to vapor of 1,2-dichlorobenzene for seven hours per day, five days per week for six to seven months at an average concentration of 560 mg/m^3. No adverse effects were noted in behavior, growth, organ weights, hematology, or gross and microscopic examination of tissues. In a nine-month chronic toxicity study Varshavskaya (1967), gave rats 1,2-dichlorobenzene at daily doses of 0.001, 0.01, and 0.1 mg/kg. The toxicological observations in the highest dose group was anemia and other blood changes, liver damage, and central nervous system depression. Liver damage has also been observed with rats and guinea pigs exposed to 1,4-dichlorobenzene at a concentration of 2,050 mg/m^3 for

six months (Hollingsworth, et al. 1956). There have been no specific studies on the chronic effects of 1,3-dichlorobenzene, although this compound may have been a contaminant in the preparations of the other two isomers used for toxicological testing (U.S. EPA, 1979).

E. Other Relevant Information

Dichlorobenzenes can induce the microsomal drug metabolizing enzymes. Changes in the levels of microsomal enzymes can affect the metabolism and biological activity of a wide variety of xenobiotics (Ware and West, 1977).

V. AQUATIC TOXICITY

A. Acute Toxicity

Acute studies have indicated that the position of the chlorine atoms on the benzene ring do not dramatically influence the toxicity of dichlorobenzenes for freshwater fish. In 96-hour static bioassays with bluegills, Leomis macrohirus, LC_{50} values were 4,280, 5,590 and 5,020 µg/l for 1,4-, 1,2, and 1,3-dichlorobenzene, respectively (U.S. EPA, 1978). However, Dawson, et al. (1977) has provided a 96-hour static LC_{50} value of 27,000 µg/l for 1,2-dichlorobenzene for the same species. A greater range of toxicities was obtained for the freshwater invertebrate Daphnia magna tested in 96-hour static bioassays. LC_{50} values were: 2,440; 11,000; and 28,100 µg/l for the 1,2-, 1,4-, and 1,3-dichlorobenzene isomers, respectively (U.S. EPA, 1978). Marine fish were slightly more resistant than freshwater fish in 96-hour static assays with LC_{50} values ranging from 17,400 to 9,660 µg/l for 1,4- and 1,2-dichlorobenzene, respectively, for the sheepshead minnow. Marine invertebrates were the most sensitive organisms

tested with LC_{50} values of 1,970, 1,990, and 2,850 µg/l obtained for 1,2-, 1,4-, and 1,3- dichlorobenzenes respectively in mysid shrimp (Mysidopsis bahia) (U.S. EPA, 1978).

B. Chronic Toxicity

The only chronic study performed was an embryo-larval test of the freshwater fish, the fathead minnow (Pimephales promelas), that produced a chronic value of 1,000 µg/l. No other chronic studies were available.

C. Plant Effects

The freshwater algae Selenastrum capricornutum, when tested for the effects of dichlorobenzenes on chlorophyll a and cell numbers, had effective concentrations ranging from 91,600 to 98,000; 149,000 to 179,000; and 96,700 to 98,100 µg/l for 1,2-, 1,3-, and 1,4-dichlorobenzene, respectively. Similar studies in the marine algae Skeletonema costatum revealed effective concentrations of 44,100 to 44,200; 49,600 to 52,800; and 54,800 to 59,100 for 1,2-, 1,3-, and 1,4-dichlorobenzenes.

D. Residues

Bioconcentration factors of 89, 66, and 60 were obtained for 1,2-, 1,3-, and 1,4-dichlorobenzenes in the bluegill. Data on marine bioconcentration factors are not available.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The Occupational Safety and Health Administration, (OSHA, 1976), and the American Conference of Governmental Industrial Hygienists (ACGIH, 1977) threshold limit value is 300 mg/m^3 for 1,2-dichlorobenzene and 450 mg/m^3 for 1,4-dichlorobenzene. The acceptable daily intake (ADI) of 1,2- or 1,4-dichlorobenzene is 1.316 mg/day (Natl. Acad. Sci., 1977). There are

no standards for 1,3-dichlorobenzene. The U.S. EPA (1979) draft water quality criterion for total dichlorobenzene (all three isomers) is 0.16 mg/l.

B. Aquatic

The draft criteria for the protection of freshwater organisms are 44 µg/l not to exceed 99 µg/l for 1,2-dichlorobenzene; 310 µg/l not to exceed 700 ug/l for 1,3-dichlorobenzene; and 190 µg/l not to exceed 440 µg/l for 1,4-dichlorobenzene. For marine organisms criteria have been drafted as 15 µg/l not to exceed 34 µg/l for 1,2-dichlorobenzene; 22 µg/l not to exceed 49 µg/l for 1,3-dichlorobenzene; and 15 µg/l not to exceed 34 µg/l for 1,4-dichlorobenzene.

DICHLOROBENZENES

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No. 68

3,3'-Dichlorobenzidine

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated 3,3'-dichlorobenzidine and has found sufficient evidence to indicate that this compound is carcinogenic.

3,3'-DICHLOROBENZIDINE

SUMMARY

The adverse health effects associated with 3,3'-dichlorobenzidine include the elevated risk of carcinogenicity based upon data from several experimental bioassays. Animals exposed to dust containing dichlorobenzidine were found to have a slight to moderate pulmonary congestion.

One aquatic toxicity test has been performed for dichlorobenzidine, yielding results indicating that concentrations of 0.5 µg/l were acutely toxic to a freshwater fish species.

3,3'-DICHLOROBENZIDINE

I. INTRODUCTION

This profile is based primarily on the Ambient Water Quality Criteria Document for Dichlorobenzidine (U.S. EPA, 1979). The molecular formula of 3,3'-dichlorobenzidine (4,4'-diamino-3,3'-dichlorobiphenyl) is $C_{12}H_{10}Cl_2N_2$, and has a molecular weight of 253.13. The chemical is sparingly soluble in water (0.7 g/l at 15°C), but readily soluble in organic solvents. Because of the fact that 3,3'-dichlorobenzidine is an organic base, it may be fairly tightly bound to humic materials, causing long-term storage in soils.

3,3'-Dichlorobenzidine has been demonstrated to be a carcinogen in experimental animals. Various types of sarcomas and adenocarcinomas have been induced at injection sites, and in specific organ systems upon dosage by gavage. No evidence is available implicating 3,3'-dichlorobenzidine as a human carcinogen.

II. EXPOSURE

A. Water

3,3'-Dichlorodibenzidine has been detected in water near a waste disposal lagoon ranging from 0.13 to 0.27 mg/l, as have benzidine concentrations up to 2.5 mg/l (Sikka, et al. 1978). In water of the Sumida River in Tokyo receiving effluents of dye and pigment factories (Takemura, et al. 1965) total aromatic amines including 3,3'-dichlorobenzidine were reported as high as 0.562 mg/l. The literature tends to support the possibility that the use of storage lagoons to handle 3,3'-dichlorobenzidine wastes may pose a threat to persons relying on nearby wells for drinking water.

B. Food

Data quantifying levels of 3,3'-dichlorobenzidine in foods have not been reported. It was suggested that consumption of fish would serve as the major dietary intake of 3,3'-dichlorobenzidine. No measurable levels of 3,3'-dichlorobenzidine were detected (<10 µg/l) in fish sampled near a contaminated waste-lagoon (Diachenko, 1978).

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor to be 1,150 for 3,3'-dichlorobenzidine for the edible portions of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficient.

C. Inhalation

The low volatility and large crystal structure of 3,3'-dichlorobenzidine would tend to minimize the risk of exposure to the chemical in ambient air. However, inhalation may be a major source of exposure to those individuals occupationally exposed to 3,3'-dichlorobenzidine. Concentrations as high as 2.5 mg/100 m^3 have been reported in one Japanese pigment factory (Akiyama, 1970).

D. Dermal

Under specific conditions of moist skin and high atmospheric humidity and temperature dermal absorption of 3,3'-dichlorobenzidine may be possible.

III. PHARMACOKINETICS

A. Absorption

Data concerning the rates and degree of absorption of dichlorobenzidine have not be quantitated.

B. Distribution

One study administering (^{14}C)-3,3'-dichlorobenzidine at doses of 0.2 mg/kg intravenously in rats, monkeys, and dogs revealed a general distribution of radioactivity after 14 days. The highest (^{14}C)-3,3'-dichlorobenzidine levels were found in the livers of all three species, in the bile of monkeys and in lungs of dogs (Kellner, et al. 1973).

C. Metabolism

Following the intravenous injection of 0.2 mg/kg (^{14}C)-3,3'-dichlorobenzidine, the total urinary radioactivity was recovered as one-third unchanged (^{14}C)-3,3'-dichlorobenzidine, one-third as the mono-N-acetyl derivative of the parent compound, and the remainder not recoverable (Kellner, et al., 1973). Chronic ingestion of small doses of 3,3'-dichlorobenzidine lead to the appearance of four metabolic products including benzidine (U.S. EPA, 1979), however, the results may be questionable due to the analytical methods employed in the study. No metabolites of 3,3'-dichlorobenzidine have been detected in the excreta of dogs experimentally administered the parent compound (U.S. EPA, 1979), nor the urine of human subjects experimentally administered the chemical (Gerarde and Gerarde, 1974).

E. Excretion

Several studies have indicated that fecal elimination may be a major route of excretion in animals and humans (U.S. EPA, 1979). One study (Meigs, et al. 1954) detected unspecified amounts of 3,3'-dichlorobenzidine in the urine of occupationally exposed workers.

IV. EFFECTS ON MAMMALS

A. Carcinogenicity

A number of investigations have reported the carcinogenic potential of 3,3'-dichlorobenzidine. Dietary 3,3'-dichlorobenzidine at 1,000 mg/kg have been associated with the significant occurrence of mammary adenocarcinomas, granulocytic leukemia, and zymbal gland carcinomas in male rats and mammary adenocarcinomas in female rats (Stula, et al. 1975). In dogs, oral doses of 100 mg/kg were associated with the significant occurrence of hepatic and urinary bladder carcinomas (Stula, et al. 1975). Levels of 0.5 and 1.0 mls of a 4.4 percent suspension of 3,3'-dichlorobenzidine in rat feed, resulting in a 4.53 g total dose of the chemical, produced an increase of cancers of the mammary gland, Zymbal gland, urinary bladder, skin, small intestine, liver, thyroid gland, kidney, hematopoietic system and salivary glands (Pliss, 1959). Hepatic tumors and sebaceous gland carcinoma were observed in mice exposed to a total dose of 127.5 to 135 mg over a ten month period of time (Pliss, 1959). 3,3'-Dichlorobenzidine was administered at levels of 30 mg every 3 days for 30 days by gavage. Observations over nine months demonstrated that DCB is ineffective as a mammary carcinogen (Griswold, et al. 1968). A diet of 0.3 percent 3,3'-dichlorobenzidine was marginally carcinogenetic and tumorigenic to hamsters (U.S. EPA, 1979). 3,3'-Dichlorobenzidine has also found to produce transformation in cultured rat embryo cells (Freeman, et al. 1973). Epidemiology studies in the United States, Great Britian, and Japan have not provided evidence

that 3,3'-dichlorobenzidine by itself induces bladder cancer in workers occupationally exposed to the chemical. For some studies, though, the latent period for tumor formation might not have elapsed.

B. Mutagenicity

3,3'-Dichlorobenzidine has been shown to induce frame shift mutations in Salmonella typhimurium tester strain TA1598 in the presence of the S9 NADPH-fortified rat liver enzyme preparation (Garner, et al. 1975). Similar results with tester strain TA98 indicating frame shift mutations and tester strain 1000 indicating base-pair substitutions were observed by prior metabolic activation with a male mouse enzyme system (Lazear and Louis, 1977).

C. Teratogenicity

Information relative to the teratogenic effects of 3,3'-dichlorobenzidine was not found in the available literature. Document (U.S. EPA, 1979). The chemical has been shown to cross the placental barrier and increase the incidence of leukemia in the offspring of pregnant mice given doses of 8-10 mg of 3,3'-dichlorobenzidine subcutaneously during the last week of pregnancy, but these results may represent toxic effects on neonates through suckling milk from dosed mothers (Golub, et al. 1969, 1974). Altered growth and morphology of cultured kidney tissue obtained from prenatally exposed mouse embryos has been observed (Shabad, et al. 1972; Golub, et al. 1969).

D. Toxicity

An acute oral LD_{50} for DCB in mice, given to mice for seven consecutive days was 352 mg/kg/day for females and 386 mg/kg/day for males. Single-dose LD_{50} values were reported as 488 and 676 mg/kg for female and male mice, respectively. Rats exposed to atmospheric dust containing unspecified amounts of 3,3'-dichlorobenzidine for 14 days showed no increased mortalities. Upon autopsy slight to moderate pulmonary congestion and one pulmonary abcess were observed.

V. AQUATIC TOXICITY

The only aquatic species tested for the toxic effects of 3,3'-dichlorobenzidine was the bluegill, Lepomis macrochirus. It was found to be acutely toxic at concentrations of 0.5 mg/l or greater (Sikka, et al. 1978).

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor aquatic criteria derived by U.S. EPA (1979), which are summarized below have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

The American Conference of Governmental Industrial Hygienists has recommended that exposure to 3,3'-dichlorobenzidine be reduced to zero, based on the demonstrated carcinogenicity of the chemical in experimental animals. Occupational standards have not been placed on 3,3'-dichlorobenzidine and standards regulating levels of the chemical in the environment or in food have not been proposed.

A recommended draft criterion of 1.69×10^{-2} µg/l has been established, corresponding to a lifetime cancer risk of 10^{-5}. This value was derived from data relating 3,3'-dichlorobenzidine to the daily consumption of two liters of water and 18.7 g of fish and shellfish.

B. Aquatic

Data were insufficient to draft criteria for either freshwater or marine life.

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No. 69

1,1-Dichloroethane

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

1,1-DICHLOROETHANE

Summary

There is no available evidence to indicate that 1,1-dichloroethane produces carcinogenic or mutagenic effects. A single study in rats failed to show teratogenic effects following inhalation exposure.

Symptoms produced by human poisoning include respiratory tract irritation, central nervous system depression, and marked cardiac excitation. Animal studies indicate that 1,1-dichloroethane may produce liver damage.

Sufficient toxicological data are not available to calculate aquatic exposure criteria.

1,1-DICHLOROETHANE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Chlorinated Ethanes (U.S. EPA, 1979a).

The chloroethanes are hydrocarbons in which one or more of the hydrogen atoms have been replaced by chlorine atoms. Water solubility and vapor pressure decrease with increasing chlorination, while density and melting point increase. 1,1-Dichloroethane (ethylidene dichloride; ethylidene chloride; molecular weight 98.96) is a liquid at room temperature with a boiling point of 57.3°C, a melting point of -98°C, a specific gravity of 1.1776, and a solubility in water of 5 g/liter (U.S. EPA, 1979a).

The chloroethanes are used as solvents, cleaning and degreasing agents, and in the chemical synthesis of a numoer of compounds. No commercial production of 1,1-dichloroethane has been reported in the United States (NIOSH, 1978).

The chlorinated ethanes form azeotropes with water (Kirk and Othmer, 1963). All are very soluble in organic solvents (Lange, 1956). Microbial degradation of the chlorinated ethanes has not been demonstrated (U.S. EPA, 1979a).

The reader is referred to the Chlorinated Ethanes Hazard Profile for a more general discussion of chlorinated ethanes (U.S. EPA, 1979b).

II. EXPOSURE

The chloroethanes are present in raw and finished waters due primarily to industrial discharges. Small amounts of the chloroethanes may be formed by chlorination of drinking water or treatment of sewage. Air levels of these volatile compounds are produced by evaporation during use as degreasing agents and in dry-cleaning operations (U.S. EPA, 1979a).

Sources of human exposure to chloroethanes include water, air, contaminated foods and fish, and dermal absorption. Fish and shellfish have shown levels of chloroethanes in the nanogram range (Dickson and Riley, 1976).

No information on levels of 1,1-dichloroethane in foods was found in the available literature. Sufficient data is not available to estimate a steady-state bioconcentration factor for 1,1-dichloroethane.

III. PHARMACOKINETICS

Pertinent data could not be located in the available literature on 1,1-dichloroethane for absorption, distribution, metabolism and excretion. However, the reader is referred to a more general treatment of chloroethanes (U.S. EPA, 1979b) which indicates rapid absorption of chloroethanes following oral or inhalation exposure; widespread distribution of the chloroethanes throughout the body; enzymatic dechlorination and oxidation to the alcohol and ester forms; and excretion of the chloroethanes primarily in the urine and in expired air.

Additionally, it has been indicated that the absorption of 1,1-dichloroethane is most similar to that of the 1,2-isomer (indicating significant dermal absorption as well as rapid oral or inhalation absorption).

IV. EFFECTS

A. Carcinogenicity and Mutagenicity

Pertinent data could not be located in the available literature.

B. Teratogenicity

An inhalation study in rats has indicated no major teratogenic effects of 1,1-dichloroethane (Schwetz, et al. 1974).

C. Other Reproductive Effects

Inhalation of 1,1-dichloroethane by pregnant rats produced delayed ossification of sternebrae in fetuses, indicating an effect of the compound in retarding fetal development (Schwetz, et al. 1974).

D. Chronic Toxicity

Use of 1,1-dichloroethane as an anesthetic was discontinued because of marked excitation of the heart (Browning, 1965). Poisoning cases have shown respiratory tract irritation and central nervous system depression (U.S. EPA, 1979a). Animal studies indicate that inhalation of 1,1-dichloroethane may produce liver damage (Sax, 1975).

V. AQUATIC TOXICITY

Pertinent aquatic toxicity data could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The current promulgated Occupational Safety and Health Administration exposure standard for 1,1-dichloroethane is 100 ppm, time-weighted average for up to a 10-hour work day, 40-hour work week.

Sufficient data are not available to derive a criterion to protect human health from exposure to 1,1-dichloroethane from ambient water.

B. Aquatic

Sufficient toxicologic data are not available to calculate aquatic exposure criteria.

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No. 70

1,2-Dichloroethane

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

70-1

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated 1,2-dichloroethane and has found sufficient evidence to indicate that this compound is carcinogenic.

1,2-DICHLOROETHANE

Summary

Results of an NCI carcinogenesis bioassay in rats and mice have shown that 1,2-dichloroethane may produce a wide variety of tumors, including squamous cell carcinomas, hemangiosarcomas, mammary adenocarcinomas, and hepatocellular carcinomas. Mutagenic effects have been shown in the Ames Salmonella system and in E. coli; metabolites of 1,2-dichloroethane have also shown mutagenic effects in the Ames assay.

One study has failed to indicate teratogenic effects following inhalation exposure to 1,2-dichloroethane although reproductive toxicity was demonstrated. Chronic human exposure to 1,2-dichloroethane has produced neurological symptoms and liver and kidney damage. Poisoning victims have shown diffuse dystrophic changes in the brain and spinal cord.

Acute toxicity values for freshwater organisms ranged from 431,000 to 550,000 µg/l. Marine invertebrates appeared to be somewhat more sensitive to 1,2-dichloroethane with an LC_{50} value of 113,000 µg/l reported.

1,2-DICHLOROETHANE

I. INTRODUCTION

This profile is based on the draft Ambient Water Quality Criteria Document for Chlorinated Ethanes (U.S. EPA, 1979a).

The chloroethanes are hydrocarbons in which one or more of the hydrogen atoms of ethane are replaced by chlorine atoms. Water solubility and vapor pressure decrease with increasing chlorination, while density and melting point increase. 1,2-Dichloroethane (molecular weight 98.96) is a liquid at room temperature with a boiling point of 83.4°C, a melting point of -35.4°C, a specific gravity of 1.253, and a solubility of 8.1 g/l in water (U.S. EPA, 1979a).

The chloroethanes are used as solvents, cleaning and degreasing agents, and in the chemical synthesis of a number of compounds. A large portion of 1,2-dichloroethane is used in the production of vinyl chloride and chlorinated chemicals, and as an ingredient, along with tetraethyl lead, in antiknock mixtures (U.S. EPA, 1979a).

1,2-Dichloroethane production in 1976 was $4,000 \times 10^3$ tons (U.S. EPA, 1979a). The chlorinated ethanes form azeotropes with water (Kirk and Othmer, 1963). All are very soluble in organic solvents (Lange, 1956). Microbial degradation of the chlorinated ethanes has not been demonstrated (U.S. EPA, 1979a).

The reader is referred to the Chlorinated Ethanes Hazard Profile for a more general discussion of chlorinated ethanes (U.S. EPA, 1979b).

II. EXPOSURE

The chloroethanes present in raw and finished waters are due primarily to industrial discharges. Small amounts of the chloroethanes may be formed

by chlorination of drinking water or treatment of sewage. Of 80 water samples tested, 27 contained 1,2-dichloroethane at concentrations of 0.2 to 8 µg/l (U.S. EPA, 1974).

Sources of human exposure to chloroethanes not only include water, but also air, contaminated foods and fish, and dermal absorption. For example, 1,2-dichloroethane has been detected in 11 of 17 spices in concentrations ranging from 2 to 23 µg/g of spice (Page and Kennedy, 1975). In fish and shellfish, levels of chloroethanes in the nanogram range have been found (Dickson and Riley, 1976).

The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor for 1,2-dichloroethane to be 4.6 for the edible portions of fish and shellfish consumed by Americans. This estimate was based on the measured steady-state bioconcentration studies in bluegills.

III. PHARMACOKINETICS

A. Absorption

The chloroethanes are absorbed rapidly following oral or inhalation routes of exposure (U.S. EPA, 1979a). Animal studies indicate that significant absorption of 1,2-dichloroethane may occur following dermal application (Smyth, et al. 1969).

B. Distribution

Pertinent information could not be located in the available literature on 1,2-dichloroethane. The reader is referred to more general treatment of the chloroethanes (U.S. EPA, 1979b) which indicates a widespread distribution of chloroethanes through the body.

C. Metabolism

In general, the metabolism of chloroethanes involves both enzymatic dechlorination and hydroxylation to corresponding alcohols (U.S. EPA, 1979a). Metabolism of 1,2-dichloroethane produces a variety of metabolites in the urine. The main two are: s-carboxymethylcysteine and thiodiacetic acid (Yllner, 1971a,b,c,d). Yllner (1971a,b,c,d) also stated that the percentage of 1, 2-dichloroethane metabolized decreased with increasing dose, suggesting saturation of metabolic pathways.

D. Excretion

The chloroethanes are excreted primarily in the urine and in expired air (U.S. EPA, 1979a). Animal studies conducted by Yllner (1971a,b, c,d) indicate that large amounts of chlorinated ethanes administered by i.p. injection are excreted in the urine, with very little excretion in the feces. Excretion appears to be rapid, since 90 percent of an i.p. administered dose of 1,2-dichloroethane was eliminated in the first 24 hours (U.S. EPA, 1979a).

IV. EFFECTS

A. Carcinogenicity

Results of the NCI bioassay for carcinogenicity (NCI, 1978) have indicated that 1,2-dichloroethane administration produced an increase in several types of tumors. Squamous cell carcinomas and hemangiosarcomas were produced in male rats, and mammary adenocarcinomas in female rats, following feeding of 1,2-dichloroethane. In mice, hepatocellular carcinomas in males and mammary adenocarcinomas in females were both increased after oral treatment with 1,2-dichloroethane.

B. Mutagenicity

Testing of 1,2-dichloroethane in the Ames Salmonella assay and an E. coli assay system have indicated mutagenic activity of this compound (Brem, et al. 1974). Metabolites of 1,2-dichloroethane (S-chloroethyl cysteine, chloroethanol, and chloroacetaldehyde) have shown positive mutagenic effects in the Ames system (U.S. EPA, 1979a). 1,2-Dichloroethane has also been reported to increase mutation frequencies in pea plants (Kiricheck, 1974) and Drosophila (Nylander, et al. 1978).

C. Teratogenicity

Inhalation studies with 1,2-dichloroethane in pregnant rats did not indicate teratogenic effects (Vozovaya, 1974).

D. Other Reproductive Effects

Rats exposed to 1,2-dichloroethane by inhalation showed reduced litter sizes, decreased live births, and decreased fetal weights (Vozovaya, 1974).

E. Chronic Toxicity

Patients suffering from 1,2-dichloroethane poisoning have shown diffuse dystrophic changes in the brain and spinal cord (Akimov, et al. 1978). Chronic exposures have produced neurologic changes and liver and kidney impairment (NIOSH, 1978a).

Animal studies with 1,2-dichloroethane toxicity have shown liver and kidney damage and fatty infiltration, and some bone marrow effects (U.S. EPA, 1979a).

F. Acute Toxicity

Oral human LD_{Lo} (lowest dose which has caused death) values have been estimated at 500 and 810 mg/kg in two studies (NIOSH, 1978b). Other species show a similar sensitivity to 1,2-dichloroethane, except for the

rat. An LD_{50} value for this species has been estimated to be 12 µg/kg (NIOSH, 1978b).

V. AQUATIC TOXICITY

A. Acute Toxicity

Acute 96-hour static LC_{50} values ranged from 431,000 to 550,000 µg/l for the bluegill (Lepomis macrochirus), while a single 48- hour static LC_{50} value of 218,000 µg/l was obtained for the freshwater cladoceran Daphnia magna (U.S. EPA, 1978). A single acute marine invertebrate study was available, reporting a 96-hour static LC_{50} value of 113,000 µg/l for the mysid shrimp (Mysidopsis bahia) (U.S. EPA, 1978).

B. Chronic Toxicity and Plant Effects

Pertinent information could not be located in the available literature on chronic toxicity and plant effects.

C. Residues

A bioconcentration factor of 2 has been reported for the bluegill (U.S. EPA, 1979a).

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

Based on the NCI carcinogenesis bioassay data, and using a linear, nonthreshold model, the U.S. EPA (1979a) has estimated a level of 1,2-dichloroethane in ambient water that will result in an additional cancer risk of 10^{-5} to be 7 µg/l.

The 8-hour TWA exposure standard developed by OSHA for 1,2-dichloroethane is 50 ppm.

B. Aquatic

In freshwater environment a criterion has been drafted for 1,2-dichloroethane as 3,900 µg/l as a 24-hour average, not to exceed 8800 µg/l. For marine life, the criterion has been drafted as 880 µg/l, not to exceed 2000 µg/l.

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No. 71

1,1-Dichlorethylene

Health and Environmental Effects

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

1,1-DICHLOROETHYLENE

Summary

Ambient levels of 1,1-dichloroethylene have not been determined. The primary effect of acute and chronic occupational exposure to 1,1-dichloroethylene is depression of the central nervous system. In experimental animals, both liver and kidney damage have been noted after exposure, regardless of the route of administration. 1,1-Dichloroethylene has been shown to be a mutagen in bacterial systems and a carcinogen in mice. Both kidney adenocarcinomas and mammary adenocarcinomas were produced after exposure to 1,1-dichloroethylene by inhalation. No teratogenic effects have been observed.

For freshwater fish, the reported 96-hour LC_{50} values range from 73,900 to 108,000 µg/l 1,1-dichloroethylene. Reported 48-hour EC_{50} values for Daphnia magna range from 11,600 to 79,000 µg/l. 96-Hour LC_{50} values of over 224,000 µg/l have been observed for saltwater fish and invertebrates. An embryo-level test with freshwater fish resulted in an adverse effect occurring at 2,800 µg/l. Algae, both fresh and saltwater, apparently are not affected by concentrations of 1,1-dichloroethylene as high as 716,000 µg/l.

1,1-DICHLOROETHYLENE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Dichloroethylenes (U.S. EPA, 1979a).

1,1-Dichloroethylene ($C_2H_2Cl_2$; molecular weight 96.95) is a clear colorless liquid used as a chemical intermediate in the synthesis of methylchloroform and in the production of polyvinylidene chloride copolymers (PVCDs). Prior to 1976, annual production of 1,1-dichloroethylene was approximately 120,000 metric tons (Arthur D. Little, Inc., 1976). 1,1-Dichloroethylene has the following physical/chemical properties: water solubility of 2,500 µg/ml, vapor pressure 591 mm Hg, and a melting point of -122.1°C. For more general information regarding the dichloroethylenes, the reader is referred to the EPA/ECAO Hazard Profile on Dichloroethylenes (U.S. EPA, 1979b).

II. EXPOSURE

A. Water

The National Organic Monitoring Survey (U.S. EPA, 1978a) reported detecting 1,1-dichloroethylene in finished drinking waters; however, neither the amount nor the occurrence was quantified.

B. Food

Pertinent data could not be located in the available literature on the ingestion of 1,1-dichloroethylene in foods. The U.S. EPA (1979a) has estimated the weighted bioconcentration factor for 1,1-dichloroethylene to be 6.9 for the edible portions of fish and shellfish consumed by Americans. This estimate was based on the octanol/water partition coefficient of 1,1-dichloroethylene.

C. Inhalation

The population at risk due to vinylidene chloride exposure is composed primarily of workers in industrial or commercial operations manufacturing or using it. Airborne emissions of vinylidene chloride are not likely to pose a significant risk to the general population. Emissions during production, storage, and transport can be controlled by methods similar to those planned for control of vinyl chloride (Hushon and Kornreich, 1978).

III. PHARMACOKINETICS

A. Absorption

Specific data on the absorption of dichloroethylenes are unavailable. However, a recent study by McKenna, et al. (1978b) suggests that in rats most, if not all, of the orally administered dose is absorbed at two dose levels: 1 and 50 mg/kg.

B. Distribution

Distribution of 1,1-dichloroethylene was studied in rats following inhalation (Jaeger, et al. 1977). The largest concentrations were found in kidney, followed by liver, spleen, heart, and brain, and fasting made no difference in the distribution pattern. At the subcellular level 1,1-dichloroethylene or its metabolites appear to bind to macromolecules of the microsomes and mitochondria (Jaeger, et al. 1977). There is also some association with the lipid fraction.

C. Metabolism

In the intact animal, a large portion of the systemically absorbed 1,1-dichloroethylene is metabolically converted, with 36 percent appearing in the urine of rats within 26 hours (Jaeger, et al. 1977). The essential

feature of 1,1-dichloroethylene metabolism is the presence of epoxide intermediates, which are reactive and may form covalent bonds with tissue macromolecules (Henschler, 1977). In rats and mice, covalently bound metabolites are found in the kidney and liver (McKenna, et al. 1978b). Interaction of 1,1- dichloroethylene with the microsomal mixed function oxidase system is not clear, since both inhibitors (dithiocarbamate) and inducers (phenobarbital) decreased the toxic effects of the compound (Anderson and Jenkins, 1977; Reynolds, et al. 1975; Jenkins, et al. 1972). However, Carlson and Fuller (1972) reported increased mortality from 1,1-dichloroethylene in rats following phenobarbital pretreatment. There is evidence that the 1,1-dichloroethylene metabolites are conjugated with glutathione, which presumably represents a detoxification step (McKenna, et al. 1978a).

D. Excretion

It is speculated that 1,1-dichloroethylene has a rapid rate of elimination, since a substantial fraction of the total absorbed dose may be recovered in the urine within 26 to 72 hours (Jaeger, et al. 1977; McKenna, et al. 1978a). Also, disappearance of covalently bonded metabolites of 1,1-dichloroethylene (measured as TCA-insoluble fractions) appears to be fairly rapid, with a reported half-life of 2 to 3 hours (Jaeger, et al. 1977).

IV. EFFECTS

A. Carcinogenicity

1,1-Dichloroethylene has been shown to produce kidney adenocarcinomas in male mice and mammary adenocarcinomas in female mice upon inhalation of 100 mg/m^3 (Maltoni, 1977; Maltoni, et al. 1977). In similar experiments with Sprague-Dawley rats exposed up to 800 mg/m^3, no significant increase in tumor incidence was noted. Also, hamsters exposed to the same

conditions as the mice failed to exhibit an increased tumor incidence (Maltoni, et al. 1977). In rats exposed to 1,1-dichloroethylene in their drinking water (200 mg/l), there was no evidence of increased tumors (Rampy, et al. 1977). There was an increased incidence of mammary tumors in rats receiving 20 mg of 1,1-dichloroethylene by gavage 4 to 5 days a week for 52 weeks. The incidence was 42 percent in the treated animals and 34 percent in the controls; however, the data was not analyzed statistically (Maltoni, et al. 1977).

B. Mutagenicity

1,1-Dichloroethylene has been shown to be mutagenic in S. typhimurium (Bartsch, et al. 1975) and E. coli K12 (Greim, et al. 1975). In both systems, mutagenic activity required microsomal activation. In mammalian systems, 1,1-dichloroethylene was negative in the dominant lethal assay (Short, et al. 1977b; Anderson, et al. 1977).

C. Teratogenicity

A study by Murrary, et al. (1979) failed to show teratogenic effects in rats or rabbits inhaling concentrations of up to 160 ppm 1,1-dichloroethylene for 7 hours per day or in rats given drinking water containing 200 ppm 1,1-dichloroethylene.

D. Other Reproductive Effects

Pertinent data could not be located in the available literaure.

E. Chronic Toxicity

In animal studies, liver damage is associated with exposure, either in the air or water, to 1,1-dichloroethylene (6 $\mu g/m^3$ or 0.79 $\mu g/l$) with transitory damage appearing as vacuolization in liver cells. In both guinea pigs and monkeys, continuous exposure to 1,1-dichloroethylene produced increased mortality, while intermittent exposure to the same concentration in

air produced no increase in mortality (U.S. EPA, 1979a). Less attention has been paid to the renal toxicity of 1,1-dichloroethylene despite the occurrence of histologically demonstrated damage at exposures equal to or less than those required for hepatotoxicity (Predergast, et al. 1967; Short, et al. 1977a).

F. Other Relevant Information

Alterations in tissue glutathione concentrations affect the hepatotoxicity of 1,1-dichloroethylene, with decreased tissue glutathione associated with greater toxicity and elevated glutathione associated with decreased toxicity (Jaeger, et al. 1973,1977).

V. AQUATIC TOXICITY

A. Acute Toxicity

Dill, et al. calculated, for the fathead minnow, Pimephales promelas, 96-hour LC_{50} values of 169,000 µg/l using static techniques and 108,000 µg/l using flow-through tests with measured concentrations. The reported 96-hour LC_{50} value for the bluegill, Lepomis macrochirus, is 73,900 µg/l in a static test (U.S. EPA, 1978b). Two 48-hour tests with Daphnia magna resulted in EC_{50} values of 11,600 and 79,000 ug/l, respectively (Dill, et al.; U.S. EPA, 1978b). The 96-hour LC_{50} values for the sheepshead minnow, Cyprinodon variegatus, and the tidewater silverside, Menidia beryllina, are 249,000 and 250,000 µg/l, respectively (U.S. EPA, 1978b; Dawson, et al. 1977). The 96-hour LC_{50} for the mysid shrimp, Mysidopsis bahia, is reported to be 224,000 µg/l (U.S. EPA, 1978b).

B. Chronic Toxicity

An embryo-larval test with the fathead minnow resulted in no adverse effects occurring at 2,800 µg/l, the highest test concentration (U.S. EPA, 1978b).

C. Plant Effects

The 96-hour EC_{50} value based on cell numbers of the freshwater alga, Selenastrum capricornutum, is reported to be greater than 798,000 µg/l (U.S. EPA, 1978b). The effective concentration of 1,1-dichloroethylene on the saltwater alga, Skeletonema costatum, was observed to be 712,000 µg/l (U.S. EPA, 1978b).

D. Residues

Pertinent data could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The American Conference of Governmental Industrial Hygienists (ACGIH, 1977) threshold limit value (TLV) for 1,1-dichloroethylene is 40 mg/m^3, with calculated daily exposure limits of 286 mg/day. 1,1-Dichloroethylene is suspected of being a human carcinogen; and using the "one-hit" model, the U.S. EPA (1979a) has estimated levels of 1,1-dichloroethylene in ambient water which will result in specified risk levels of human cancer:

Exposure Assumptions (per day)	Risk Levels with Corresponding Draft Criteria		
	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish.	0.013 µg/l	0.13 µg/l	1.3 µg/l
Consumption of fish and shellfish only.	0.21 µg/l	2.1 µg/l	21 µg/l

B. Aquatic

For 1,1-dichloroethylene, the drafted criterion to protect freshwater aquatic life is 530 µg/l as a 24-hour average, not to exceed 1,200 µg/l at any time. No saltwater criterion has been proposed because of insufficient data.

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No. 72

trans-1,2-Dichloroethylene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

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TRANS-1,2-DICHLORETHYLENE

SUMMARY

There is little specific information available on trans-1,2-dichloroethylene. This compound is quantitatively less toxic than the 1,1-dichloroethylene isomer; however, the toxicity appears qualitatively the same with depression of the central nervous system as well as liver and kidney damage. Trans-1,2-dichloroethylene has been shown to be a mutagen in bacterial systems. The teratogenicity and carcinogenicity of this compound have not been evaluated.

In the only aquatic study reported, the observed 96-hour LC_{50} value for the bluegill is 135,000 µg/l in a static bioassay.

TRANS-1,2-DICHLORETHYLENE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Dichloroethylenes (U.S. EPA, 1979).

Trans-1,2-dichloroethylene (traans 1,2-DCE; $C_2H_2Cl_2$; molecular weight 96.95) is a clear colorless liquid. Since the early 1960's trans-1,2-dichloroethylene has had no wide industrial usage (Patty, 1963). Trans-1,2-dichloroethylene has the following physical/chemical properties: water solubility of 6,300 µg/ml, a vapor pressure of 324 mm Hg, and a melting point of -50°C (Patty, 1963).

II. EXPOSURE

A. Water

Trans-1,2-dichloroethylene was found at a concentration of 1 µg/l in Miami drinking water (U.S. EPA, 1975, 1978).

B. Food

Pertinent data could not be located in the available literature on the ingestion of trans-1,2-dichloroethylene in foods. The U.S. EPA (1979) has not estimated a bioconcentration factor for trans-1,2-dichloroethylene.

C. Inhalation

Pertinent information could not be located in the available literature.

III. PHARMACOKINETICS

A. Absorption

Animal or human studies do not appear to exist which specifically document the degree of systemic absorption of trans-1,2-dichloroethylene by any route.

B. Distribution

Pertinent data could not be located in the available literature.

C. Metabolism

Trans-1,2-dichloroethylene is metabolized through an epoxide intermediate to either a dichloroacetaldehyde or monochloroacetic acid (Liebman and Ortiz, 1977). The epoxide intermediate which is reactive, may form covalent bonds with tissue macromolecules (Henschler, 1977). Metabolism of the cis-isomer relative to the amount taken up by the liver was much greater than the trans-isomer (McKenna, et al. 1977).

D. Excretion

Pertinent data could not be located in the available literature.

IV. EFFECTS

A. Carcinogenicity

Pertinent data could not be located in the available literature.

B. Mutagenicity

Trans-1,2-dichloroethylene has been shown to be negative in the E. coli K12 and Salmonella mutagenicity assays (Greim, et al. 1975; Cerna and Kypenova, 1977).

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C. Teratogenicity and Other Reproductive Effects

Pertinent information could not be located in the available literature.

D. Chronic Toxicity

Although little data is available specifically on trans-1,2-dichloroethylene, it appears that chronic exposure results in kidney and liver damage similar to that noted with 1,1-dichloroethylene (U.S. EPA, 1979). Jenkins, et al. (1972) found trans-1,2-dichloroethylene to be considerably less potent than 1,1-dichloroethylene.

V. AQUATIC TOXICITY

A. Acute Toxicity

The reported 96-hour LC_{50} value for the bluegill, Lepomis macrochirus, exposed to 1,2-dichloroethylene is 135,000 µg/l (U.S. EPA, 1979) in a static test procedure.

B. Chronic Toxicity, Plant Effects and Residues

Pertinent information could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The American Conference of Governmental Industrial Hygienists (ACGIH, 1977) threshold limit value (TLV) for 1,2-dichloroethylene is 790 mg/m^3, with calculated daily exposure limits of 5,643 mg/day. The U.S. EPA (1979) draft Water Quality Criteria Document for Dichloroethylene states that human health criterion could not be derived due to the lack of sufficient data on which to base a criterion.

B. Aquatic

Guidelines do not exist for salt water species because of insufficient data. The draft criterion to protect freshwater aquatic life is 530 µg/l as a 24-hour average and not to exceed 1200 µg/l at any time (U.S. EPA, 1979).

TRANS 1,2-DICHLOROETHYLENE

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No. 73

Dichloroethylenes

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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DICHLOROETHYLENES

Summary

Of the three dichloroethylene isomers, cis 1,2-dichloroethylene, trans 1,2-dichloroethylene, and 1,1-dichloroethylene, only the 1,1-dichloroethylene isomer is produced in large quantities. Most of the health effects information available is related to the 1,1-dichloroethylene isomers; however, qualitatively the toxicity of the 1,2-dichloroethylene isomers appears to be similar, with depression of the central nervous system and liver and kidney damage. Of the three isomers, 1,1-dichloroethylene is the most toxic. Both 1,1-dichloroethylene and trans 1,2-dichloroethylene are mutagenic in bacterial systems. Only 1,1-dichloroethylene has been shown to be a carcinogen.

All of the available aquatic data, with one exception, are for 1,1-dichloroethylene. Reported 96-hour LC_{50} values for the bluegill are 73,900 and 135,500 µg/l, respectively, for 1,1-dichloroethylene and 1,2-dichloroethylene. Two observed 48-hour LC_{50} values for Daphnia exposed to 1,1-dichloroethylene range were 11,600 and 79,000 µg/l. All saltwater fish and invertebrates tested with 1,1-dichloroethylene showed 96-hour LC_{50} values over 224,000 µg/l, and all algae tested both in fresh and saltwater, had 96-hour EC_{50} values (based on cell numbers) of 716,000 µg/l and over. In the only reported chronic study, no adverse effects were observed at the highest test concentration of 2,800 µg/l for fathead minnows exposed to 1,1-dichloroethylene.

DICHLOROETHYLENES

I. INTRODUCTION

This profile is based on the draft Ambient Water Quality Criteria Document for Dichloroethylenes (U.S. EPA, 1979).

The dichloroethylenes ($C_2H_2Cl_2$; molecular weight 96.95) consist of the three isomers: 1,1-dichloroethylene, cis- 1,2-dichloroethylene, and trans-1,2-dichloroethylene. Dichloroethylenes are clear colorless liquids with water solubilities between 2,500 and 6,300 µg/l, vapor pressures between 591 and 208 mm Hg, and melting points between -50°C and -122°C (U.S. EPA, 1979). The 1,1-dichloroethylene isomer is the most extensively used in industry, with annual production prior to 1976 of approximately 120,000 metric tons (Arthur D. Little, Inc., 1976). The 1,1-dichloroethylene isomer is used as a chemical intermediate in the synthesis of methylchloroform and in the production of polyvinylidene chloride copolymers (PVDCs).

II. EXPOSURE

A. Water

The National Organic Monitoring Survey (U.S. EPA, 1978a) reported detecting 1,1-dichloroethylene in finished drinking waters; however, neither the amount nor the occurrence was quantified. Both cis and trans-1,2-dichloroethylene were found at concentrations of 16 and 1 µg/l, respectively, in Miami drinking water (U.S. EPA, 1975, 1978b).

B. Food

Pertinent data could not be located on the ingestion of dichloroethylene in foods. The U.S. EPA (1979) has estimated the weighted bioconcentration factor for 1,1-dichloroethylene to be 6.9 for the edible portions of

fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficients of 1,1-dichloroethylene. There is no estimate for a bioconcentration factor for the other isomers.

C. Inhalation

The population at risk due to vinylidene chloride exposure is composed primarily of workers in industrial or commercial operations manufacturing or using it. Airborne emissions of vinylidene chloride are not likely to pose a significant risk to the general population. Emissions during production, storage, and transport can be controlled by methods similar to those planned for control of vinyl chloride (Hushon and Kornreich, 1978)

III. PHARMACOKINETICS

A. Absorption

Specific data on the absorption of dichloroethylenes are unavailable. However, a recent study by McKenna, et al. (1978b) suggests that in rats most, if not all, of the orally administered dose is absorbed at two dose levels: 1 and 50 mg/kg.

B. Distribution

Distribution of 1,1-dichloroethylene was studied in rats following inhalation (Jaeger, et al. 1977). The largest concentrations were found in kidney, followed by liver, spleen, heart, and brain; and fasting made no difference in the distribution pattern. At the subcellular level 1,1-dichloroethylene or its metabolites appear to bind to macromolecules of the microsomes and mitochondria (Jaeger, et al. 1977). There is also some association with the lipid fraction. Distl,2-dichloroethylene isomers are not available.

C. Metabolism

The essential feature of all dichloroethylene metabolism is the presence of epoxide intermediates which are reactive and may form covalent

bonds with tissue macromolecules (Henschler, 1977). In rats and mice, covalently bound metabolites of 1,1-dichloroethylene are found in the kidney and liver (McKenna, et al. 1978b). Interaction of dichloroethylenes with the microsomal mixed function oxidase system is not clear, since both inhibitors (dithiocarbamate) and inducers (phenobarbital) decreased the toxic effects of 1,1-dichloroethylene (Anderson and Jenkins, 1977; Reynolds, et al. 1975; Jenkins, et al. 1972). Carlson and Fuller (1972), however, reported increased mortality from 1,1-dichloroethylene in rats following phenobarbital pretreatment. There is evidence that the 1,1-dichloroethylene metabolites are conjugated with gluthathione, which presumably represents a detoxification step (McKenna, et al. 1978b).

B. Excretion

The only information available on elimination pertains to the 1,1-dichloroethylene isomer. It is postulated that the 1,1-dichloroethylene isomer has a rapid rate of elimination since a substantial fraction of the total absorbed dose may be recovered in urine within 26 to 72 hours (Jaeger, et al. 1977; McKenna, et al. 1978a). Also, disappearance of covalently bonded metabolites of 1,1-dichloroethylene (measured as TCA-insoluble fractions) appears to be fairly rapid, with a reported half-life of 2 to 3 hours (Jaeger, et al. 1977).

IV. EFFECTS

A. Carcinogenicity

There is only data on the carcinogenicity of the 1,1-dichloroethylene isomer. This isomer has been shown to produce kidney adenocarcinomas in male mice and mammary adenocarcinomas in female mice upon inhalation of 100 mg/m^3 (Maltoni, et al. 1977; Maltoni, 1977). In

similar experiments with Sprague-Dawley rats exposed as high as 800 mg/m^3, no significant increase in tumor incidence was noted. Hamsters exposed to the same conditions as the mice failed to exhibit an increased tumor incidence (Maltoni, et al. 1977). In rats exposed to 1,1-dichloroethylene in their drinking water (200 mg/l) there was no evidence of increased tumors (Rampy, et al. 1977). There was an increased incidence of mammary tumors in rats receiving 20 mg of 1,1-dichloroethylene by gavage 4 to 5 days a week for 52 weeks. The incidence was 42 percent in the treated animals and 34 percent in the controls; however, the data was not analyzed statistically (Maltoni, et al. 1977).

B. Mutagenicity

1,1-Dichloroethylene has been shown to be mutagenic in S. typhimurium (Bartsch, et al. 1975) and E. coli K12 (Greim, et al. 1975); however, both the cis and trans isomers of 1,2-dichloroethylene were non-mutagenic when assayed with E. coli K12. In order to demonstrate mutagenic activity, 1,1-dichloroethylene needed microsomal activation. In addition, cis 1,2-dichloroethylene was mutagenic in Salmonella tester strains, and promoted chromosomal aberrations in cytogenic analysis of bone marrow cells (Cerna and Kypenova, 1977). In mammalian systems, 1,1-dichloroethylene was negative in the dominant lethal assay (Short, et al. 1977b; Anderson, et al. 1977).

C. Teratogenicity

A study by Murray, et al. (1979) failed to show teratogenic effects in rats or rabbits inhaling concentrations of up to 160 ppm 1,1-dichloroethylene for 7 hr/day or in rats given drinking water containing 200 ppm 1,1-dichloroethylene.

D. Other Reproductive Effects

Pertinent data could not be located in the available literature.

E. Chronic Toxicity

In animal studies, liver damage is associated with exposure either in the air or water, to dichloroethylenes (6 mg/m^3 or 0.79 mg/l) with transitory damage appearing as vacuolization in liver cells (U.S. EPA, 1979). Jenkins, et al. (1972) found both cis and trans 1,2-dichloroethylene to be considerably less potent than 1,1-dichloroethylene as a hepatotoxin. Less attention has been paid to the renal toxicity of the dichloroethylenes despite the occurrence of histologically demonstrated damage at 1,1-dichloroethylene exposures equal to or less than those required for hepatoxicity (Prendergast, et al. 1967; Short, et al. 1977a).

F. Other Relevant Information

Alterations in tissue glutathione concentrations affect the hepatotoxicity of 1,1-dichloroethylene, with decreased tissue glutathione associated with greater toxicity and elevated gluthathione associated with decreased toxicity (Jaeger, et al. 1973, 1977).

V. AQUATIC TOXICITY

A. Acute Toxicity

All of the available data for dichloroethylene, with one exception, are for 1,1-dichloroethylene. The data on acute static tests with bluegill, Lepomis macrochirus, under similar conditions show a correlation between the degree of chlorination and toxicity. The 96-hour LC_{50} values for the bluegill are 73,900 and 135,000 ug/l for 1,1- and 1,2-dichloroethylene, respectively. Additional data for other ethylene chlorides are as follows: 44,700 ug/l for trichloroethylene, and 12,900 ug/l for tetrachloroethylene (U.S. EPA, 1978c). These results indicate an increase in the lethal effect on bluegills with an increase in chlorine content.

The 96-hour LC_{50} value for the sheepshead minnow, Cypuimocen variegatus, tidewater silverside, Menidia beryllina, and mysid shrimp, Mysidepsis behia, following exposure to 1,1-dichloroethylenes are all over 224,000 ug/l (U.S. EPA, 1978c).

B. Chronic Toxicity

In the only reported chronic study, an embryo-larval test in fathead minnows, no adverse effects were observed at the highest test concentration of 1,1-dichloroethylene, 2800 µg/l (U.S. EPA, 1979).

C. Plant Effects

The 96-hour EC_{50} values based on cell numbers of the freshwater algae, Salenestrum capricornutum and the saltwater algae, Skeletonema costatum, are 798,000 and 712,000 µg/l, respectively, for exposure to 1,1-dichloroethylene (U.S. EPA, 1978c).

D. Residues

Pertinent information could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The American Conference of Governmental Industrial Hygienists (ACGIH, 1977) threshold limit values (TLV) are 40 mg/m^3 (1,1-dichloroethylene) and 790 mg/m^3 (1,2-dichloroethylene). These values allow daily exposures of 286 mg 1,1-dichloroethylene per day and 5,643 mg 1,2-dichloroethylene per day. The U.S. EPA (1979) draft water criteria document for dichloroethylene states that no human health criterion could be derived for cis- and trans-1,2-dichloroethylene due to the lack of sufficient data on which to base a criterion. 1,1-dichloroethylene is suspected of

being a human carcinogen, and using the "one-hit" model, the U.S. EPA (1979) has estimated levels of 1,1-dichloroethylene in ambient water which will result in specified risk levels of human cancer:

Exposure Assumptions (per day)	Risk levels and Corresponding Draft Criteria		
	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish	0.013 ug/l	0.13 ug/l	1.3 ug/l
Consumption of fish and shellfish only.	0.11 ug/l	2.1 ug/l	21 ug/l

B. Aquatic

The proposed draft criterion to protect freshwater species from dichloroethylene toxicity are as follows (U.S. EPA, 1979):

Compound	24-hr. Average	Concentration not to be exceeded at anytime
1,1-dichloroethylene	530 ug/l	1,200 ug/l
1,2-dichloroethylene	620 ug/l	1,400 ug/l
For saltwater species:		
1,1-dichloroethylene	1,700 ug/l	3,900 ug/l
1,2-dichloroethylene	Not available	Not available

DICHLOROETHYLENES

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No. 74

Dichloromethane

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

October 30, 1980

DISCLAIMER

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DICHLOROMETHANE (DCM)

SUMMARY

In humans, DCM is a central nervous system depressant resulting in narcosis at high concentrations, and impaired task performance. Dichloromethane is metabolized to carbon monoxide and causes an increase in carboxyhemoblogin, placing persons with cardiovascular disease, and perhaps those who are pregnant, at increased risk of disease. On the basis of present evidence, DCM cannot be firmly identified as an animal or human carcinogen. DCM has been shown to be mutagenic to Salmonella, but not to S. cerevisia and Drosophila, and causes cell transformation.

Aquatic organisms are fairly resistant to dichloromethane, with acute toxicity values ranging from 193,000 to 331,000 ug/l.

DICHLOROMETHANE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Documert for Halomethanes (U.S. EPA, 1979a).

Dichloromethane (CH_2Cl_2, methylene chloride, methylene dichloride, and methylene bichloride; molecular weight 84.93) is a colorless liquid with a melting point of -95.1°C, a boiling point of 40°C, a specific gravity of 1.327 g/ml at 20°C, a vapor pressure of 362.4 mm Hg at 20°C, and a solubility in water of 13.2 g/l at 25°C. Dichloromethane is a common industrial solvent found in insecticides, metal cleaners, paints, and paint and varnish removers (Balmer, et al., 1976). In 1976, 244,129 metric tons were imported (U.S. EPA, 1977). For additional information regarding the halomethanes as a class, the reader is referred to the Hazard Profile on Halomethanes (U.S. EPA, 1979b).

II. EXPOSURE

A. Water

The U.S. EPA (1975) has identified dichloromethane in finished drinking waters in the U.S. in 8 of 83 sites, with a maximum level of 0.007 mg/l and a median of less than 0.001 mg/l. The dichloromethane in drinking water is not a product of water chlorination (U.S. EPA, 1975; Morris and McKay, 1975). In the national organics monitoring survey, dichloromethane was detected in 15 of 109 sites, with a mean concentration (positive results only) of 0.0061 mg/l (U.S. EPA, 1978).

B. Food

Pertinent information could not be located in the available literature.

C. Inhalation

Reported background concentrations of dichloromethane in both continental and saltwater atmospheres were about 0.00012 mg/m^3, and urban air concentrations ranged from less than 0.00007 to 0.00005 mg/m^3. Local indoor concentrations can be high due to the use of aerosol sprays or solvents (Natl. Acad. Sci., 1978).

III. PHARMACOKINETICS

A. Absorption

Efficiences of absorption of dichloromethane by the lungs are between 30 to 75 percent, depending on length of exposure, concentration, and activity level (Natl. Acad. Sci., 1978; Natl. Inst. Occup. Safety and Health, 1976).

B. Distribution

Upon inhalation and absorption, dichloromethane levels increase rapidly in the blood to equilibrium levels that depend primarily upon atmosphere concentration (Natl. Acad. Sci., 1978). Carlsson and Hultengren (1975) reported that dichloromethane and its metabolites were in highest concentrations in white adipose tissue, followed in descending order by levels in brain and liver.

C. Metabolism

Dichloromethane is metabolized to carbon monoxide. Some of this carbon monoxide is exhaled, but a significant amount

is involved in the formation of carboxyhemoglobin (Natl. Inst. Occup. Safety and Health, 1976). Cardiorespiratory stress from elevated carboxyhemoglobin may be greater as a result of dichloromethane exposure than from exposure to carbon monoxide alone due to the continued formation of carbon monoxide following cessation of dichloromethane exposure (Stewart and Hake, 1976). As shown by animal experiments, other possible human metabolites of dichloromethane include carbon dioxide, formaldehyde, and formic acid (Natl. Acad. Sci., 1978).

D. Excretion

A large proportion of absorbed dichloromethane is excreted unchanged, primarily via the lungs, with some in the urine. DiVincenzo, et al. (1972) have reported that about 40 percent of absorbed dichloromethane undergoes some reaction and decomposition process in the body.

IV. EFFECTS

A. Carcinogenicity

Friedlander et al. (1978) analyzed the mortality of Eastman-Kodak male employees exposed to low levels of methylene chloride. No significant neoplastic risk factors were identified.

Theiss and coworkers (1977) examined the tumorigenic activity of dichloromethane in strain A mice. Dichloromethane at the low dose (1:5 dilution of the maximum tolerated dose) produced marginally significant increases in tumor response. Shimkin and Stoner (1975) did not report a positive carcinogenic response for the strain A mouse bioassay system.

Although the data base is inadequate, there is a basis to suspect the potential carcinogenicity of DCM based on the (marginally positive) pulmonary adenoma response in strain A mice, on positive responses for mutagenicity in the Ames test, and on the ability to transform rat embryo cells (see below).

B. Mutagenicity

Simmon, et al. (1977) reported that dichloromethane was mutagenic to Salmonella typhimurium strain TA100 when assayed in a dessicator whose atmosphere contained the test compound. Metabolic activation was not required, and the number of revertants per plate was directly dose-related. A linear dose response curve was observed. Dichloromethane did not increase mitotic recombination in S. cerevisia D3 (Simmon, et al., 1977), and it was reported negative on testing for mutagenicity in Drosophila (Filippova, et al., 1967). Positive results for dichloromethane in the Ames assay were recently confirmed by Jongen, et al. (1978) with vapor phase exposures (5,700 ppm) of strains TA98 and TA100.

C. Teratogenicity

Schwetz et al., (1975) showed that DCM can affect embryonal and fetal development in rats and mice as evidenced by the increased incidence of extra sternebrae. DCM also affects the development of chick embryos, causing a 2 to 3-fold increase in malformation frequencies (Elsavaara et al., 1979).

D. Other Reproductive Effects

Gynecologic problems in femal workers exposed for

long period to gasoline and dichloromethane vapors were reported by Vozovaya (1974). Also, inhalation exposures of rats and mice to vapor levels of 4,342 mg/m^3 for seven hours daily on gestation days 6 to 15 produced evidence of feto- or embryotoxicity (Schwetz, et al., 1975; Natl. Inst. Occup. Safety and Health, 1976).

E. Chronic Toxicity

Acute exposures to dichloromethane produce central nervous system disfunction, are irritating to mucous membranes, and increase the level of carboxyhemoglobin (Natl. Acad. Sci., 1978). Price, et al. (1978) reported that Fischer rat embryo cells (F1706) were transformed by dichloromethane at high concentrations (1.6×10^{-3}M) in the growth medium. However, Sivak (1978) indicated the presence of carcinogenic contaminants in the dichloromethane and could not demonstrate transformation in the BALB/C-3T3 assay system with highly purified food grade dichloromethane.

V. AQUATIC TOXICITY

A. Acute Toxicity

Acute toxicity values have been obtained for two species of freshwater fish and one species of freshwater invertebrates. LC_{50} values for the fathead minnow (Pimephales promelas) ranged from 193,000 ug/l in a flowthrough assay to 310,000 ug/l in a static assay. An LC_{50} value of 224,000 ug/l was obtained for the bluegill (Lepomis Macrochirus) in a static assay. Daphnia magna were reported as having an LC_{50} value of 224,000 ug/l (U.S. EPA,

1979a). For the marine fish, the sheepshead minnow (Cyprinodon variegatus), an LC_{50} of 331,000 ug/l was obtained. The marine mysid shrimp was reported as having an LC_{50} value of 256,000 ug/l.

B. Chronic Toxicity

Chronic tests for freshwater or marine species could not be located in the available literature.

C. Plant Effects

Both species of freshwater algae, Selenastrum capricornutum and marine algae, Skeletonema cornutum, were equally resistant to dichloromethane, with LC_{50} values in excess of 662,000 ug/l.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by the U.S. EPA (1979a), which are summarized below, have gone through the process of public review, therefore, there is a possibility that these criteria will be changed.

A. Human

OSHA (1976) has established an eight-hour, time-weighted average for dichloromethane of 1,737 mg/m^3; however, NIOSH (1976) has recommended a ten-hour, time-weighted average exposure limit of 261 mg/m^3. The U.S. EPA (1979a) draft water quality criterion for dichloromethane is 2 ug/l. The reader is referred to the Halomethanes Hazard Profile for discussion of criteria derivation (U.S. EPA, 1979b).

B. Aquatic

The criterion for protecting freshwater aquatic life has been drafted as 4,000 ug/l, not to exceed 9,000 ug/l, while the marine criterion has been drafted as 1,900 ug/l, not to exceed 4,400 ug/l.

DICHLOROMETHANE

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LB-45-01
No. 75

2,4 - Dichlorophenol

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

October 1, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may reflect all available information impacts presented by the subject chemical. This document has undergone scrutiny to ecsure its technical accuracy.

2,4-DICHLOROPHENOL

Summary

Insufficient data exist to indicate that 2,4-dichlorophenol is a carcinogenic agent. 2,4-Dichlorophenol appears to act as a nonspecific irritant in promoting tumors in skin painting studies. No information on mutagenicity, teratogenicity, or chronic toxicity is available. In a subacute study, the only adverse effect noted in mice was microscopic nonspecific liver changes. 2, 4-Dichlorophenol appears to be a weak uncoupler of oxidative phosphorylation.

Acute and chronic toxic effects of 2,4-dichlorophenol have been observed at a concentrations as low as 2,200 and 365 ug/l respectively. Mortality to early life stages of one species of fish occurs at 70 ug/l. Flavor impairment studies indicate that the highest concentrations of 2,4-dichlorophenol in water which would not cause tainting of the edible portions of fish range from 0.4 to 14 ug/l depending on the species of fish consumed.

2,4-DICHLOROHENOL (2,4 DCP)

I. INTRODUCTION

This profile is in large part based on the Ambient Water Quality Criteria Document for 2,4-dichlorophenol (U.S. EPA,1980).

2,4-Dichlorophenol is a colorless, crystalline solid having the empirical formula $C_6H_4Cl_2O$ and a molecular weight of 163.0 (Weast, 1975). It has the following physical and chemical properties (Sax, 1975; Aly and Faust, 1965; Weast, 1975; Kirk and Othmer, 1964):

Melting Point:	45° C
Boiling Point:	210° C at 760 mm Hg
Vapor Pressure:	1.0 mm Hg at 53.0° C
Solubility:	slightly soluble in water at neutral pH; dissolves readily in ethanol and benzene

2,4-DCP is a commercially produced, substituted phenol used entirely as an intermediate in the manufacture of industrial and agricultural products such as the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D), germicides, and miticides.

Little data exists regarding the persistence of 2,4-dichlorophenol in the environment. It is a product resulting from degradation of many commercial products by plants, micro-organisms, and sunlight. Its low vapor pressure cause it to be only slowly removed from surface water via volatilization (U.S. EPA, 1980). Studies have indicated low absorption of 2,4-DCP from natural surface waters by various clays (Aly and Faust, 1964). 2,4-DCP is photolabile in aqueous solutions (Aly and Faust, 1964; Crosby and Tutass, 1966) and can be degraded to succinic

acid by microorganisms in soil and water (Alexander and Aleem, 1961; Ingols, et al., 1966; Loos, et al., 1967). In lake water, under laboratory conditions, the half life of 2,4-DCP is 8-9 days in aerated waters and 17 days under anaerobic conditions (U.S. EPA 1980).

II. EXPOSURE

A. Water

Sources of 2,4-DCP in water are agricultural run-off (as a contaminant and metabolic breakdown product of biocides) and manufacturing waste discharges (U.S. EPA, 1980). Recent experiments under conditions simulating the natural environment have not demonstrated that 2,4-dichlorophenol is a significant product resulting from chlorination of phenol-containing wastes (Glaze, et al. 1978; Jolley, et al. 1978). The worst-case exposure to 2,4 DCP from drinking water, as calculated from 2,4-DCP level in water downstreams from a 2,4-DCP manufacturing facility, has been estimated as 36 ug/kg body weight/day.

B. Food

Contamination of food with 2,4-DCP could be an indirect result from use of the herbicide 2,4-D (U.S. EPA, 1980). The worst use estimate for the degree of human exposure to 2,4-DCP from consumption of contaminated meat is about 4 ug 2,4-DCP/kg body weight.

The U.S. EPA (1980) has estimated the weighted average bioconcentration factor for 2,4-dichlorophenol to be 41 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficient.

C. Inhalation

Pertinent information regarding direct evidence indicating that humans are exposed to significant amounts of 2,4-dichlorohenol through inhalation has not been found in the available literature.

III. Absorption

Pertinent information regarding the absorption of 2,4-dichlorophenol in humans or animals was not found in the available literature, although data on toxicity indicate that 2,4-dichlorophenol is absorbed after oral administration (Deichmann, 1943; Kobayashi, et al. 1972). Due to its high lipid solubility and low ionization at physiological pH, 2,4-dichlorophenol is expected to be readily absorbed after oral administration (U.S. EPA, 1979).

B. Distribution

Pertinent information dealing directly with tissue distribution after 2,4-dichlorophenol exposure was not found in the available literature. Feeding of 2,4-D (300 - 2000 ug/g feed) to cattle and sheep (Clark, et al. 1975) and Nemacide (50 - 800 ug/g feed) to laying hens (Sherman, et al. 1972) did not produce detectible residues of 2,4-dichlorophenol in muscle or fat. Cattle and sheep had high levels of 2,4-dichlorophenol in kidney and liver; hens had detectible levels of 2,4-dichlorophenol in liver and yolk.

C. Metabolism

Pertinent information dealing directly with metabolism of administered 2,4-dichlorophenol was not found in the available literature. In mice, urinary metabolites of ^{14}C-labelled gamma

or beta benzene hexachloride (hexachlorocylohexane) included 2,4-dichorophenol and its glucuronide and sulfate conjugates (as 4-6 percent of total metabolites) (Kurihara, 1975).

D. Excretion

Pertinent information dealing with excretion of administered 2,4-dichlorophenol was not found in the available literature. After oral administration of 1.6 mg Nemacide to rats over a 3-day period, 67 percent of that compound appeared in urine as 2,4-dichlorophenol within 3 days. With a dosage of 0.16 mg Nemacide, 70 percent of the compound appeared in urine as 2,4-dichlorophenol within 24 hours (Shafik, et al. 1973).

IV. EFFECTS

A. Carcinogenicity

Existing data are not sufficient to indicate whether 2,4-dichlorophenol is a carcinogen. The only study performed (Boutwell and Bosch, 1959) indicate that 2,4-dichlorophenol may promote skin cancer in mice after initiation with dimethylbenz-anthracene. An analysis of the data of Boutwell and Bosch using the Fisher Exact Test indicated that the incidence of papillomas. in 2,4-DCP-treated groups was significantly elevated over controls, while the incidence of carcinomas was not (U.S. EPA, 1980).

B. Mutagenicity, Teratogenicity and Other Reproductive Effects

No studies addressing the mutagenicity, teratogenicity or other reproductive effects of 2,4-DCP in mammaliam systems were found in the available literature. However, genotoxic effects of 2,4-DCP have been reported in plants. Exposure of

flower buds or root cells of vetch (Vicia fabia) to solutions of 2,4-DCP, 01M and 62.5 mg/l, respectively, caused meiotic and mitotic changes including alterations of chromosome stickiness, lagging chromosome anaphase bridges and fragmentation (Amer and Ali, 1968, 1969, 1974). The relationship of such changes in plant cells to potential changes in mammalian cells has not been established (U.S. EPA, 1980).

C. Chronic Toxicity

One report (Bleiberg, et al. 1964) suggested that 2,4-dichlorophenol was involved in the induction of chloracne and porphyria cutanea tarda in workers manufacturing 2,4-dichlorophenol and 2,4,5-trichlorophenol. Since various chlorinated dioxins (powerful chloracnegens) have been implicated as contaminants of 2,4,5-trichlorophenol, the specific role of 2,4-dichlorophenol in causing chloracne and porphyria is not conclusive (Huff and Wassom, 1974).

In a study (Kobayaski, et al. 1972) in which male mice were fed 2,4-dichlorophenol at estimated daily doses of 45, 100, and 230 mg/kg body weight, no adverse effects were noted except for some microscopic nonspecific liver changes after the maximum dose. Parameters evaluated included body and organ weights and food consumption, as well as hematological and histological changes.

D. Other Relevant Information

2,4-DCP is a weak uncoupler of oxidative phosphorylation (Farquharson, et al. 1958; Mitsuda, et al. 1963). Values on odor

threshold for 2,4-DCP in water range from 0.65 to 6.5 ug/l, depending on the temperature of water (Hoak, 1957).

V. AQUATIC TOXICITY

A. Acute Toxicity (U.S. EPA, 1980)

Two 96-hour assays have been performed examining the acute effects of 2,4-dichlorophenol in freshwater fish. An LC_{50} value of 2,020 ug/l for the bluegill, Lepomis macrochirus, and an LC_{50} value of 8,230 ug/l for the juvenile fathead minnow, Pimpephales promelas, have been reported. Two studies on the freshwater cladoceran, Daphnia magna, have produced 48-hour static LC_{50} values of 2,610 and 2,600 ug/l.

Only one marine fish or invertebrate species has been tested for the acute effects of 2,4-DCP: the mountain bass, a species endemic to Hawaii is poisoned at 20 mg 2,4-DCP/l.

B. Chronic Toxicity

Data for the chronic effects of 2,4-DCP for either freshwater or marine organisms were not located in the available literature.

C. Plant Effects

Concentrations of 2,4-DCP causing a 56 percent reduction in photosynthetic oxygen production or a complete destruction of chlorophyll were 50 or 100 mg/l, respectively, in algal assays with Chlorella pyrenoidosa. An earlier study reported that 58.3 mg 2,4-D/l caused a 50 percent reduction in Chlorophyll in the duckweed, Lemna minor. No marine plant species have been examined.

D. Residues

A bioconcentration factor of 130 has been estimated from the octanol-water partition coefficient of 2,4-dichlorophenol for aquatic organisms having a lipid content of eight percent. The estimated weighted average bioconcentraion factor for the edible portion of aquatic organisms is 41.

E. Miscellaneous

Flavor impairment studies indicated that the highest concentration of 2,4-DCP in the exposure water which would not cause tainting of the edible portion of fish ranged from 0.4 ug/l for the largemouth bass (Microbterus salmoides), to 14 ug/l for the bluegill (Lepomis marcrochirus). The value for the rainbow trout (Salmo gairdneri) was 1 ug/l.

A. Human

Based upon the prevention of adverse organoleptic effected, the criterior for 2,4-DCP in water recommended by the U.S. EPA (1980) is 0.3 ug/l. This level is far below minimal no-effect concentrations determined in laboratory animals (U.S. EPA, 1980). 3.09 mg/l is the criterion based on toxicity data (U.S. EPA, 1980).

B. Aquatic

The criterion for protecting freshwater organisms is 2020 ug/l (acute) and 365 ug/l as a chronic exposure value. No criterion was derived for marine organisms (U.S. EPA, 1980).

2,4-DICHLOROPHENOL

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No. 76

2,6-Dichlorophenol

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C.

OCTOBER 30, 1980

76-1

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

2,6-DICHLOROPHENOL

SUMMARY

There is no available information on the possible carcinogenic, teratogenic, or adverse reproductive effects of 2,6-dichlorophenol.

The compound did not show mutagenic activity in the Ames assay. A single report has indicated that 2,6-dichlorophenol produced chromosome aberrations in rat bone marrow cells; details of this study were not available for evaluation.

Prolonged administration fo 2,6-dichlorophenol may produce hepatoxic effects. Pertinent data on the toxicity of 2,6-dichlorophenol to aquatic organisms were not found in the available literature. However, EPA/ECAO Hazard Profiles on related compounds may be consulted, including metachlorophenol, 2,4,5-trichlorophenol, and 2,3,4,6-tetrachlorophenol.

I. INTRODUCTION

2,6-Dichlorophenol (2,6-DCP), CAS registry number 87-65-0, exists as white needles and has a strong penetrating odor resembling o-chlorophenol. It has the following physical and chemical constants (Weast, 1972; Hawley, 1971):

Formula:	$C_6H_4Cl_2O$
Molecular Weight:	163
Melting Point:	68°C - 69°C
Boiling Point:	219°C - 220°C (740 torr)
Vapor Pressure:	1 torr @ 59.5°C
pH:	6.79
Production:	unknown

2,6-DCP is produced as a by-product from the direct chlorination of phenol. It is used primarily as a starting material for the manufacture of trichlorophenols, tetrachlorophenols, and pentachlorophenols (Doldens, 1964).

II. EXPOSURE

A. Water

Phenols occur naturally in the environment and chlorophenols are associated with bad taste and odor in tap water (Hoak, 1957). 2,6-DCP has a taste and odor threshold of 0.002 mg/l and 0.003 mg/l, respectively (McKee and Wolf, 1963). Piet and DeGrunt (1975) found unspecified dichlorophenols in Dutch surface waters at 0.01 to 1.5 ug/l, and Burttschell, et al. (1959) demonstrated that chlorination of phenol-containing water produced, among other products, 2,6-DCP in a 25-percent yield after 18 hours of reaction.

B. Food

Pertinent data could not be located in the available literature.

C. Inhalation

Olie, et al. (1977) reported finding dichlorophenols in flue gas condensates from municipal incinerators. The levels were not quantified.

D. Dermal

Pertinent data could not be located in the available literature; however, it is known that dichlorophenols are less toxic by skin contact than mono-chlorophenols and less likely to be absorbed through the skin (Doldens, 1964).

III. PHARMACOKINETICS

A. Absorption

Pertinent data could not be located in the available literature. By comparison with other chlorophenols, it is expected that 2,6-DCP is absorbed through the skin and from the gastrointestinal tract, and rapidly eliminated (U.S. EPA, 1980).

B. Distribution

Pertinent data could not be located in the available literature. The high lipid solubility of the compound would suggest that the unexcreted and unmetabolized compound distributes to adipose tissues.

C. Metabolism and Excretion

Pertinent data could not be located in the available literature. By comparison with other chlorophenols, it is

expected that 2,6-DCP is rapidly eliminated from the body, primarily as urinary sulfate and glucuronide conjugates (U.S. EPA, 1980).

IV. EFFECTS

A. Carcinogencity

Pertinent data could not be located in the available literature.

B. Mutagenicity

2,6-DCP did not show mutagenic activity in the Ames assay (Rasanen, et al. 1977). Chromosome aberrations in rat bone marrow cells have been observed following compound administration (route and dosage not indicated) (Chung, 1978).

C. Teratogenicity and Other Reproductive Effects

Pertinent data could not be located in the available literature.

D. Chronic Toxicity

Administration of 2,6-DCP to rats (route and dosage not specified) has been reported to produce hepatic degeneration (Chung, 1978).

E. Other Relevant Information

<u>In vitro</u> tests have indicated that 2,6-DCP inhibits liver mitochondrial respiration (level not specified) (Chung, 1978). At relatively high concentrations 2,6-DCP affects the nervous system (U.S. EPA, 1980).

V. AQUATIC TOXICITY

A. Acute

McLeese, et al. (1979) reported a 52-hour lethal threshold limit of 19,100 ug/l for marine shrimp (Crangon septemspinosa) exposed to 2,6-DCP.

B. Chronic Toxicity, Plant Effects and Residues

Pertinent data could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

Based on the organoleptic properties of 2,6-DCP, a water quality criterion of 0.2 ug/l has been recommended by the U.S. EPA (1980).

B. Aquatic

No existing criteria to protect fresh and saltwater organisms were found in the available literature.

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No. 77

2,4-Dichlorophenoxyacetic Acid (2,4-D)

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

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2,4-DICHLOROPHENOXYACETIC ACID

Summary

Oral administration of 2,4-Dichlorophenoxyacetic acid (2,4-D) failed to produce carcinogenic effects in mice or dogs; however, feeding technical grade 2,4-D did produce tumors in a study with rats. Subcutaneous administration of the isooctyl ester of 2,4-D has been reported to produce reticulum cell sarcomas in mice.

A single study has indicated that 2,4-D produced mutagenic effects in Saccharomyces. Other investigations have failed to show mutagenic effects of the compound Salmonella, Drosophila, Saccharomyces, or the dominant lethal assay with mice.

2,4-D and several of its esters failed to show teratogenic effects in mice; the propylene glycol butyl ether ester of the compound produced an increase in cleft palates in this study. Studies in hamsters orally administered 2,4-D and derivatives showed teratogenic effects. Oral administration of 2,4-D to rats failed to indicate teratogenicity in one study; another investigation using oral administration of 2,4-D to rats found teratogenic effects. A three-generation feeding study of 2,4-D to rats indicated fetotoxic effects at a dosage of 1,500 ppm.

Toxicity tests on a variety of aquatic organisms generally have demonstrated that various esters of 2,4-D are more toxic than the 2,4-D acid, dimethyl amine, or sodium salt. Freshwater trout and bluegill sunfish were adversely affected by the propylene glycol butylether (PGBE) ester at concentrations of 900 to 2,000 µg/l. Daphnids and freshwater seed shrimp were sensitive to the PGBE ester at concentrations of 100 to 300 µg/l. Chronic exposure of several species of fish to concentrations up to 310 µg/l has not demonstrated any toxic effect.

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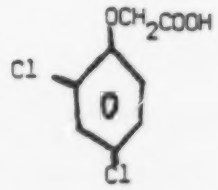
2,4-DICHLOROPHENOXYACETIC ACID

I. INTRODUCTION

2,4-Dichlorophenoxyacetic acid, CAS Registry number 94-75-7, commonly known as 2,4-D, is a white or slightly yellow crystalline compound which is odorless when pure. 2,4-D has the following physical and chemical properties (Herbicide Handbook, 1979):



Formula:	$C_8H_6Cl_2O_3$
Molecular Weight:	221.0
Melting Point:	135°C-138°C (technical); 140°C-141°C (pure)
Boiling Point:	160°C @ 0.4 torr
Density:	1.565^{30}
Vapor Pressure:	0.4 torr @ 160°C
Solubility:	Acetone, alcohol, dioxane ether, isopropyl alcohol; slightly soluble in benzene, solubility in water 0.09g/100g, H_2O
Production:	Unknown

2,4-D is used as an herbicide along with its various salts and esters, which vary its solubility properties. It is used mainly to control broad-leafed plants in pastures, and right-of-ways, and, and to keep lakes and ponds free of unwanted submersed and emersed weeds.

II. EXPOSURE

A. Water

No estimates of average daily uptake of 2,4-D from water are available; however, after treatment for water milfoil in reservoirs in

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Alabama and Tennessee, the Tennessee Valley Authority found the concentration at downstream monitoring stations to be 2 ppb. 2,4-D was not found in the harvested beans of red Mexican bean plants after irrigation with contaminated water (Gangst, 1979).

B. Food

The Food and Drug Administration, in monitoring milk and meat for residues of 2,4-D from 1963 to 1969, found no trace of the herbicide in 13,000 samples of milk and 12,000 samples of meat (Day, et al. 1978). Cattle and sheep which were fed 2,000 ppm of 2,4-D for 28 days had less than 0.05 ppm 2,4-D in the fat and muscle tissue and no detectable amount of 2,4-dichlorophenol. After seven days withdrawal from the 2,4-D diet, these tissue levels were drastically reduced (Clark, et al. 1975). Six species of fish were monitored for three weeks after the water in a pond was treated with a 2,4-D ester. The highest tissue concentration reached was 0.24 ppm eight days after application. Subsequently, the herbicide or its metabolite was eliminated rapidly. Clams and oysters accumulate more 2,4-D than do fish and crabs. Residue peaks occur from 1 to 9 days after application and then rapidly decline (Gangst, 1979).

C. Inhalation

Pertinent data were not found in the available literature; however, some 2,4-D esters which are much more volatile than the parent compound have been monitored in air up to 0.13 $\mu g/m^3$ (Farwell, et al. 1976; Stanley, et al. 1971).

D. Dermal

Pertinent data were not found in the available literature.

III. PHARMACOKINETICS

A. Absorption

Human absorption of 2,4-D following oral intake is extensive; Kohli et al. (1974) have determined absorption of 75 to 90 percent of the total dietary intake of the compound. Animal studies have indicated that the gastrointestinal absorption of 2,4-D esters may be less efficient than that of the free acid or salt form of the compound (NRCC, 1978).

B. Distribution

The phenoxy herbicides are readily distributed throughout the body tissues of mammals. Tissue levels of herbicide may be higher in the kidney than in the blood; liver and muscle show levels lower than those determined in the blood (NRCC, 1978). Withdrawal of dietary compound produced almost complete tissue loss of residues in seven days (Clark, et al. 1975).

Small amounts of phenoxy herbicides are passed to the young through the mother's milk (Bjerke, et al. 1972). Transplacental transfer of 2,4-D has been reported in mice (Lindquist and Ullberg, 1971).

C. Metabolism

Sauerhoff, et al. (1976) determined that following oral administration of 2,4-D to human volunteers, the major amount excreted in the urine was free compound; a smaller amount was excreted as a conjugate. Tissue analysis of sheep and cattle fed 2 4-D have shown unchanged compound and 2,4-dichlorophenol to be present (Clark, et al. 1975).

D. Excretion

Elimination of orally administered 2,4-D by humans is primarily through the urine (95.1 percent of the initial dose); the half-life of the compound in the body has been estimated as 17.7 hours (Sauerhoff, et.al. 1976). Clark, et al. (1964) have reported urinary elimination of 96 percent

of an oral dose of labelled 2,4-D within 72 hours by sheep; approximately 1.4 percent of the administered dose was eliminated in the feces.

The plasma half-life of 2,4-D has been estimated to be from 11.7 to 33 hours in humans (NRCC, 1978).

IV. EFFECTS

A. Carcinogenicity

Innes, et al. (1969) reported no significant increase in tumors following feeding of mice with 2,4-D for 18 months. A two-year feeding study in rats did indicate an increase in total tumors in females and malignant tumors in males following feeding of technical 2,4-D; a parallel study with dogs fed technical compound did not show carcinogenic effects (Hansen, et al. 1971).

Mice were administered maximum tolerated doses of 2,4-D and its butyl, isopropyl, and isooctyl esters in a long-term carcinogenicity study. Carcinogenic effects were seen after subcutaneous administration of the isooctyl ester (reticulum cell sarcomas) (NCI, 1968).

B. Mutagenicity

No mutagenic effects of 2,4-D in tests with Salmonella, Saccharomyces, or Drosophila were observed (Fahrig, 1974). Siebert and Lemperle (1974) have reported mutagenic effects following treatment of Saccharomyces cerevisiae strain D4 with aqueous 2,4-D solution (1,000 mg/l).

Gavage or intraperitoneal administration of 2,4-D to mice failed to show mutagenic effects in the dominant lethal assay (Epstein, et al. 1972).

C. Teratogenicity

Testing of 2,4-D and its n-butyl, isopropyl, and isooctyl esters in pregnant mice produced no significant teratogenic effects. There was a

significant increase in cleft palate deformities after administration of the propylene glycol butyl ether ester of 2,4-D (Courtney, 1974).

Subcutaneous injection of the two isopropyl esters and the isooctyl ester of 2,4-D in pregnant mice has been reported to produce teratogenic effects (Caujolle, et al. 1967), although the DMSO vehicle used is, itself, a teratogen. Bage, et al. (1973) have also reported teratogenic effects in mice following injection of 2,4-D.

Oral administration of 2,4-D to hamsters resulted in the production of some terata (Collins and Williams, 1971). Studies with rats reported that oral administration of the parent compound or its isooctyl and butyl esters, and butoxy ethanol and dimethylamine salts, produced teratogenic effects (Khera and McKinley, 1972). However, Schwetz, et al. (1971) were unable to show teratogenic effects in rats following the oral administration of 2,4-D or its isooctyl or propylene glycol butyl ether esters.

D. Other Reproductive Effects

Embryotoxic effects following subcutaneous administration of 2,4-D to pregnant mice have been reported (Caujolle, et al. 1967; Bage, et al. 1973).

Fetotoxic effects of the compound and its esters have been reported after oral administration of maximally tolerated doses (Schwetz, et al. 1971; Khera and McKinely, 1972).

Results of a three-generation study of rats fed 2,4-D indicate that at dietary levels up to 500 ppm, no reproductive effects are produced; at levels of 1,500 ppm, a decrease in survival and body weights of weanlings was observed (Hansen, et al. 1971). Bjorklund and Erne (1966) reported no adverse reproductive effects in rats fed 1,000 mg/l 2,4-D in drinking water.

E. Chronic Toxicity

Animal studies with prolonged oral administration of 2,4-D or its amine salt have indicated renal and hepatic effects (Bjorklund and Erne, 1971; Bjorn and Northen, 1948); the chemical purity of the material administered is not known. A feeding study in rats has reported histopathological liver changes at dietary levels of 2,4-D equivalent to 50 mg/kg (Dow Chemical, 1962).

V. AQUATIC TOXICITY

A. Acute Toxicity

The National Research Council of Canada (1978) has reviewed the toxic effects of 2,4-D to fish. For the bluegill sunfish (Lepomis macrochirus), 2,4-D acid and 2,4-D dimethyl amine produced toxic effects at concentrations greater than 100,000 µg/l. At 2,4-D concentrations of 50,000 µg/l or less, no increased mortalities were reported except in pink salmon. The isopropyl, butyl, ethyl, butoxy ethanol, and PGBE esters produced 48-hour LC_{50} values of 900, 1,300, 1,400, 2,100, and from 1,000 to 2,100 µg/l, respectively.

For other fish species, the results follow a similar trend in that the esters tend to be more toxic than other formulations. Meehan, et al. (1974) conducted tests of various formulations of 2,4-D on coho salmon fry and fingerlings (Oncorhycus Kitutch), chum salmon fry (O. keta), pink salmon fry (O. gorbuscha), sockeye salmon smolts (O. nerka), Dolly Varden (Salvelinus malma), and rainbow trout (Salmo gairdneri). The butyl ester was the most toxic ester tested, with concentrations of 1,000 µg/l or greater producing nearly 100 percent mortalities in all species tested. The PGBE ester was similar in toxicity to the butyl ester. Rainbow trout were reported to have shown a 48-hour LC_{50} value of 1,100 µg/l on exposure to

the PGBE ester of 2,4-D. Harlequin fish (Rasbora heteromorpha) showed a 48-hour LC_{50} value of 1,000 µg/l on exposure to the butoxyethyl ester of 2,4-D (National Research Council of Canada 1978). Rehwoldt, et al. (1977) have observed 96-hour LC_{50} values of 26,700; 40,000; 70,100; 70,700; 94,600; 96,500; and 300,600 µg/l for banded killifish (Fundulus diaphanus), white perch (Roccus americanus), stripped bass (Morone sazatilis), guppies (Libistes reticulatus), pumpkinseed sunfish (Lepomis gibbosus), carp (Cyprinus carpio), and American eel (Anguilla rostrata), respectively, exposed to commercial technical grade 2,4-D.

Sanders (1970) conducted a comparative study on the toxicities of various formulations of 2,4-D for six species of freshwater crustaceans. The PGBE ester was generally most toxic, while the dimethylamine salt was least toxic. The crayfish (Orconectes nails) was the most resistant species tested, with 48-hour static LC_{50} values greater than 100,000 µg/l for all formulations tested. The waterflea (Daphnia magna) and seed shrimp (Cypridopsis vidua) were most sensitive to the PGBE ester, with 48-hour LC_{50} values of 100 and 320 µg/l, respectively. Scuds (Gammarus fasciatus), sowbugs (Ascellus brevicaudus), and freshwater grass shrimp (Palaemonetes kadiakensis) were also moderately sensitive, with 48-hour LC_{50} values ranging from 2,200 to 2,700 µg/l. Sanders and Cope (1968) reported a 96-hour LC_{50} value of 1,600 µg/l for stonefly naiads (Pteronarcy californica) exposed to the butoxyethanol ester of 2,4-D. Technical grade 2,4-D produced a 96-hour LC_{50} value of 14,000 µg/l. Robertson and Bunting (1976) reported 96-hour LC_{50} values ranging from 5,320 to 11,570 µg/l for copepods (Cyclops vernalis) nauplii exposed to 2,4-D as free acid. The range of 96-hour LC_{50} values for nauplii exposed to 2,4-D alkonolamine salt was 120,000 to 167,000 µg/l.

Among marine invertebrates, those of commercial significance have been examined for toxic effects on exposure to 2,4-D formulations. Butler (1965) determined the 96-hour median effective concentration based on shell growth for oysters as 140 µg/l for the PGBE ester of 2,4-D. The 2,4-D acid had no detectable effect at exposures of 2,000 µg/l for 96-hours. Butler (1963) observed paralysis of brown shrimp (Penaeus aztecus) exposed to 2,4-D acid at a concentration of 2,000 µg/l for 48-hours. Sudak and Claff (1960) found a 96-hour LC_{50} value of 5,000,000 µg/l for fiddler crabs (Uca pugmax) exposed to 2,4-D.

McKee and Wolf (1963) have reviewed the toxic effects of 2,4-D to aquatic organisms. Toxic concentrations as low as 1,000 µg/l produced a 40 percent mortality for fingerling bluegills exposed to 2,4-D butyl ester. In general, esters of 2,4-D were reported to be more toxic than sodium salts of 2,4-D.

B. Chronic Toxicity

Rehwoldt, et al. (1970) exposed several species of fish to 100 µg/l 2,4-D for ten months and observed no overt effects to any tested species. The percent reduction of brain acetylcolinesterase ranged from 16 percent in white perch to 35 percent in American eels. In breeding experiments with guppies, a 100 µg/l concentration of 2,4-D had no significant effect on the reproductive process of the species under experimental conditions. Cope, et al. (1970) examined the chronic effects of PGBE ester of 2,4-D to bluegill sunfish. Fish were exposed to the herbicide in one-eighth acre ponds containing initial concentrations of up to 10,000 µg/l. Alterations in spawning activity, and the occurrence of pathological lesions of the liver, brain, and vascular system were reported for a period of up to 84

days. Mount and Stephan (1967) exposed 1-inch fathead minnows (Pimephales promelas) to a continuous series of concentrations of the butoxyethanol ester of 2,4-D ranging from 10 to 310 µg/l for a 10-month period. No deaths of deleterious effects, including abnormal spawning activity and reduced survival of eggs from exposed fish, were observed.

In static-renewal tests, Sigmon (1979) reported that the percent pupation and the percent emergence of Chironomus larvae were significantly reduced by exposure to 1,000 or 3,000 µg/l 1,4-D (acid equivalent in Weedone LV-4 formulation).

C. Plant Effects

The genera Microcystis, Scenedesmus, Chlorella, and Nitzschia showed no toxic response when exposed to 2,000 µg/l 2,4-D Lawrence (1962). Poorman (1973) treated cultures of Euglena gracilis with concentrations of 50,000 µg/l 2,4-D for 24 hours and observed decreased growth rates. Valentine and Bingham (1974) demonstrated that at 100,000 µg/l, 2,4-D reduced the cell numbers of Scenedesmus to one percent of control levels, Chlamydomonas to 48 percent of control levels, Chlorella to 66 percent of control levels, and Euglena to 90 percent of control levels within 4 to 12 days. The bluegreen algae (Nostoc muscorum) displayed a 68-percent reduction in growth when exposed to 100 µg/l 2,4-D (Conti and Cavazzini, 1973). Singh (1974) exposed Cylindrospermum to 2,4-D sodium salt at concentrations ranging from 100,000 to 1,200,000 µg/l and reported that concentrations above 800,000 µg/l caused growth to cease completely. McKee and Wolf (1963) reviewed the effectiveness of 2,4-D in control of emergent aquatic plants and reported that concentrations ranging from 6,000 to 100,000 µg/l have been effective in controlling a number of species.

D. Residue

Cope, et al. (1970) examined residues of the PGBE ester of 2,4-D in the freshwater vascular plant, Potamogeten nodosus, in a one-eighth acre pond treated with single 100 to 10,000 µg/l applications of the chemical. A gradual depeletion of the herbicide to insignificant levels was demonstrated within three months.

Schultz and Gangstad (1976) reported that the flesh of fish exposed to 2,4-D dimethyl sodium salt in ponds treated with from 2.24 to 8.96 kg (as an acid equivalent) of the chemical did not attain the 100 µg/l level realized in the water two weeks after application.

The National Research Council of Canada (NRCC) (1978) has reviewed the bioconcentration data and associated residues of 2,4-D in a number of studies. NRCC indicated that a relatively short half-life of less than two days is found for fish and oyster. At water concentrations of 100 to 200 µg/l, the bioconcentration of 2,4-D various aquatic invertebrates was one to two orders of magnitude greater than in the water. Oysters (Crassostica virginica) were reported to have a bioconcentration factor of 180 when exposed to the butoxyethanol ester of 2,4-D. The freshwater bluegill and mosquito fish (Gambusia affinis) had bioconcentration factors ranging from 7 to 55, respective to water concentrations. Fish fed a diet containing 2,4-D bioconcentrated the 2,4-D acid by less than 0.2.

VI. EXISTING GUIDELINES

A. Human

The acceptable daily intake of 2,4-D for humans has been established at 0.3 mg/kg (FAO, 1969).

B. Aquatic

Pertinent data were not found in the available literature.

2,4-DICHLOROPHENOXYACETIC ACID

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No. 78

1,2-Dichloropropane

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

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1,2-DICHLOROPROPANE

Summary

The major environmental source of dichloropropane is from the use of a mixture of dichloropropanes and dichloropropenes as a soil fumigant. On chronic exposure of rats to dichloropropanes the only observed effect was a lack of normal weight gain. There is no evidence that dichloropropanes are carcinogens or teratogens. Dichloropropanes have produced mutations in bacteria and caused chromosomal aberrations in rats.

Aquatic toxicity tests of 1,2-dichloropropane are limited to four acute investigations. Two observed 96-hour LC_{50} values for the bluegill are 280,000 and 320,000 µg/l and the 48-hour LC_{50} value for Daphnia magna is 52,500 µg/l. A saltwater fish has a reported 96-hour LC_{50} value of 240,000 µg/l.

1,2-DICHLOROPROPANE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Dichloropropanes/Dichloropropenes (U.S. EPA, 1979).

1,2-Dichloropropane (1,2-DCP, molecular weight 112.99) is a liquid at environmental temperatures. This isomer of dichloropropane has a boiling point of 96.4°C, a density of 1.156 g/ml, a vapor pressure of 40 mm Hg at 19.4°C and a water solubility of 270 mg/100 at 20°C (U.S. EPA, 1979). Mixtures of 1,2-dichloropropane and cis-trans-1,3-dichloropropene are used as soil fumigants. For the purposes of discussion in this hazard profile document, dichloropropane refers to the 1,2-dichloropropane isomer. When heated to decomposition temperatures, 1,2-dichloropropane emits highly toxic fumes of phosgene (Sax, 1975).

II. EXPOSURE

A. Water

Dichloropropane can enter the aquatic environment as discharges from industrial and manufacturing processes, as run-off from agricultural land, and from municipal effluents. This compound was identified but not quantified in New Orleans drinking water (Dowty, et al. 1975).

B. Food

Information was not found concerning the concentration of dichloropropane in commerical foodstuffs; therefore, the amount of this compound ingested by humans through food is not known. The U.S. EPA (1979) has estimated the bioconcentration factor (BCF) of dichloropropane to be 20. This estimate is based on the octanol/water partition coefficients of dichloropropane. The weighted average BCF for edible portions of all aquatic organisms consumed by Americans is calculated to be 5.8.

C. Inhalation

Atmospheric levels of dichloropropane have not been positively determined. However, it is known that 5-10 percent of the dichloropropane which is applied to the soil as a fumigant is released to the air (Thomas and McKeury, 1973).

III. PHARMACOKINETICS

A. Absorption, Distribution and Metabolism

Pertinent data could not be located in available literature searches regarding the absorption of dichloropropane.

B. Excretion

Pertinent data could not be located in available literature searches regarding excretion of dichloropropane. In the rat, approximately 50 percent of an orally administered dose of dichloropropane was eliminated in the urine in 24 hours (Hutson, et al. 1971).

IV. EFFECTS

A. Carcinogenicity

Only one study is reported on the carcinogenicity of dichloropropane. Heppel, et al. (1948) repeatedly exposed mice (37 exposure periods) to 1.76 mg dichloropropane per liter of air. Of the 80 mice, only three survived the exposure and subsequent observation period; however, the three survivors had multiple hepatomas at the termination of the experiment (13 months of age). Due to the high mortality, an evaluation based on this study cannot be made.

B. Mutagenicity

DeLorenzo, et al. (1977) and Bignami, et al. (1977) showed dichloropropane to be mutagenic in S. typhimurium strains TA 1535 and TA 100. Dichloropropane has also been shown to cause mutations in A. nidulans

(Bignami, et al. (1977), and to cause chromosomal aberrations in rat bone marrow (Dragusanu and Goldstein, 1975).

C. Teratogenicity

Pertinent information could not be located in available literature searches regarding teratogenicity.

D. Other Reproductive Effects

Pertinent information could not be located regarding other reproductive effects.

E. Chronic Toxicity

Pertinent information could not be located in available literature searches regarding chronic toxicity studies of dichloropropane exposure in humans. In one study by Heppel, et al. (1948) rats, guinea pigs, and dogs were exposed to 400 ppm of dichloropropane for 128 to 140 daily seven hour period (given five days per week). The only effect observed was a decreased weight in rats.

V. AQUATIC TOXICITY

A. Acute Toxicity

Two observed 96-hour LC_{50} values for the bluegill, Lepomis macrochirus, upon exposure to 1,2-dichloropropane were 280,000 and 320,000 µg/l (Dawson, et al. 1977; U.S. EPA, 1978). In the only freshwater invertebrate study reported, the 48-hour LC_{50} for Daphnia magna is 52,500 ug/l (U.S. EPA, 1979). Tidewater silverside, (Menidia bevvllina), has an observed 96- hour LC_{50} of 240,000 µg/l (Dawson, et al. 1977).

B. Chronic Toxicity

Chronic data are not available for any saltwater or freshwater species.

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C. Plant Effects

The phytotoxicity of 1,2-dichloropropane has not been investigated.

D. Residues

No information available.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by the U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

The TLV for dichloropropane is 75 ppm (350 mg/m^3) (Am. Conf. Gov. Ind. Hyg., 1977). The draft water criteria for dichloropropane is 203 ug/l (U.S. EPA, 1979).

B. Aquatic

For 1,2-dichloropropane, the proposed draft criteria to protect freshwater aquatic life are 920 µg/l a 24-hour average and the concentration should not exceed 2,100 µg/l at any time. Criteria are not available for saltwater species (U.S. EPA, 1979).

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No. 79

Dichloropropane/Dichloropropenes

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

79-1

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

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DICHLOROPROPANES/DICHLOROPROPENES

SUMMARY

The major environmental source of dichloropropanes and dichloropropenes is from the use of these compounds as soil fumigants. Some mild kidney damage has been observed in rats chronically exposed to 1,3-dichlorpropene. Both dichloropropane and dichloropropene have been shown to be mutgenic in the Ames assay test. Data are not available to prove conclusively that these compounds are chemical carcinogens.

Aquatic toxicity studies suggest that the acute toxicity of the dichloropropanes decreases as the distance between the chlorine atoms increases. As an example, the reported 96-hour LC_{50} values for the bluegill, Lepomis macrochirus, for 1,1-, 1,2-, and 1,3-dichloropropane are 97,900, 280,000, and greater than 520,000 µg/l, respectively. For Daphnia magna, the corresponding reported 48-hour LC_{50} values are 23,000, 52,000, and 282,000 µg/l, respectively. Similar results have been obtained with marine organisms.

The dichloropropenes are considerably more toxic in acute exposure than the dichloropropanes. For 1,3-dichlorpropene, the 96-hour LC_{50} value for the bluegill is 6,060 µg/l compared to 520,000 µg/l for 1,3-dichloropropane. For Daphnia magna, the corresponding values are 6,150 and 282,000 µg/l, respectively. The EC_{50}, based on chlorophyll a for a freshwater alga, is 4,950 µg/l for 1,3-dichloropropene, and 48,000 for 1,3-dichloropropane. Data on measured residues could not be located in the available literature for any saltwater or freshwater species.

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I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Dichloropropanes/Dichloropropenes (U.S. EPA, 1979).

Dichloropropanes (molecular weight 112.99) and dichloropropenes (molecular weight 110.97) are liquids at environmental temperatures. Their boiling points range from 76 to 120.4°C depending on the compound and the isomer. They are slightly denser than water, with densities ranging from 1.11 to 1.22. The principal uses of dichloropropanes and dichloropropenes are as soil fumigants for control of nematodes, in oil and fat solvents, and in dry cleaning and degreasing processes (Windholz, 1976). When heated to decomposition temperatures, 1,2-dichloropropane emits highly toxic fumes of phosgene, while 1,3-dichloropropene gives off toxic fumes of chlorides (Sax, 1975). Production of mixtures of dichloropropanes/dichloropropenes approached 60 million pounds per year prior to 1975 (U.S. EPA, 1979).

II. EXPOSURE

A. Water

Dichloropropanes and dichloropropenes can enter the aquatic environment in discharges from industrial and manufacturing processes, as run-off from agricultural land, and from municipal effluents. These compounds have been identified but not quantified in New Orleans drinking water (Dowty, et al. 1975).

B. Food

Information was not found in the available literature concerning the concentrations of dichloropropanes and dichloropropenes in commercial food stuffs. Therefore, the amount of these compounds ingested by humans is not known. The U.S. EPA

(1979) has estimated the weighted average bioconcentration factors (BCFs) of dichloropropanes and dichloropropenes to range between 2.9 and 5.8 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficients of these compounds.

C. Inhalation

Atmospheric levels of dichloropropanes and dichloropropenes are not known. However, from information on loss of these compounds to the air after land application, it was estimated that, in California alone, about 72 tons (8 percent of the pesticide used) were released to the atmosphere in 1971 (Calif. State Dept. Agric. 1971).

III. PHARMACOKINETICS

A. Absorption, Distribution and Metabolism

Pertinent information regarding the absorption, distribution, and metabolism of the dichloropropanes and dichloropropenes could not be located in the available information.

B. Excretion

No human data are available on the excretion of dichloropropanes or dichloropropenes. In the rat, 80 to 90 percent of an orally administered dose of dichloropropane or dichloropropene was eliminated by all routes within 24 hours (Hutson, et al. 1971). Approximately 50 percent of the administered dose was eliminated in the urine within 24 hours.

IV. EFFECTS

A. Carcinogenicity

Information concerning the carcinogenicity of mixtures of dichloropropanes and dichloropropenes could not be located

in the available literature. However, cis-1,3-dichloropropane has produced local sarcomas at the site of repeated subcutaneous injections (Van Duuren, et al., in press). No remote treatment-related tumors were observed.

B. Mutagenicity

Mixtures of 1,2-dichloropropane and 1,3-dichloropropene are mutagenic to S. typhimurium strains TA 1535 and TA 100, as are the individual compounds. The mixture, but not the individual compounds, is also mutagenic to TA 1978 (in the presence of microsomal activation) indicating a frame-shift mutation not capable of being produced by the individual compounds.

C. Teratogenicity and Other Reproductive Effects

Pertinent information could not be located in the available literature.

D. Chronic Toxicity

Inhalation exposure of rats, guinea pigs, and dogs to 400 ppm of 1,2-dichloropropane for 128 to 140 daily 7-hour periods (5 days per week) decreased normal weight gain in rats (Heppel, et al., 1948). Inhalation exposures of rats to 3 ppm of 1,3-dichloropropene, 4 hours a day, for 125 to 130 days produced cloudy swelling in renal tubular epithelium which disappeared by 3 months after exposures ended (Torkelson and Oyen, 1977).

V. AQUATIC TOXICITY

A. Acute Toxicity

Exposures of bluegill, Lepomis macrochirus, to 1,1-, 1,2-, and 1,3-dichloropropane under similar conditions yielded 96-hour LC_{50} values of 97,900, 280,000, and greater than 520,000

mg/l, respectively (U.S. EPA, 1978). These data suggest that toxicity decreases as the distance between the chlorine atoms increases. A reported 96-hour LC_{50} for 1,3-dichloropropene is 6,060 µg/l for the bluegill, approximately two orders of magnitude lower than for 1,3-dichloropropane (U.S. EPA, 1979). Under static test conditions, reported 48-hour LC_{50} values for 1,1-, 1,2-, and 1,3-dichloropropanes are 23,000, 52,500 and 282,000 µg/l, respectively, (U.S. EPA, 1978) for the only freshwater invertebrate species tested, Daphnia magna. The 48-hour LC_{50} value for 1,3-dichloropropene and Daphnia magna under static conditions is 6,150 µg/l (U.S. EPA, 1978).

The 96-hour LC_{50} values for the saltwater sheepshead minnow, Cyprinodon variegatus, exposed to 1,3-dichloropropane and 1,3-dichloropropene were 86,700 µg/l and 1,770 µg/l, respectively (U.S. EPA, 1978). Dawson, et al. (1977) obtained a 96-hour LC_{50} of 240,000 µg/l for the tidewater silverside, Menidia beryllina, for exposure to 1,2-dichloropropane.

For Mysidopsis bahia, the 96-hour LC_{50} for 1,3-dichloropropene was one-thirteenth that for 1,3-dichloropropane, i.e., 790 µg/l and 10,300 µg/l, respectively (U.S. EPA, 1978).

B. Chronic Toxicity

Chronic studies are limited to one freshwater study and one saltwater study. In an embryo-larval test, the chronic value for fathead minnows, Pimephales promelas, exposed to 1,3-dichloropropene was 122 µg/l (U.S. EPA, 1978). The chronic value for mysid shrimp, Mysidopsis bahia, was 3,040 µg/l for 1,3-dichloropropane in a life cycle study (U.S. EPA, 1978).

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C. Plant Effects

For 1,3-dichloropropene, the 96-hour EC_{50} values, based on chlorophyll a concentrations and cell numbers of the freshwater alga, Selenastrum capricornutum, were 4,950 µg/l and 4,960 µg/l, respectively. The respective values obtained for 1,3-dichloropropane were 48,000 and 72,200 µg/l. Thus, the propene compound is much more toxic than the propane compound, as is true for the bluegill and Daphnia magna.

D. Residues

Measured steady-state bioconcentration factors (BCF) are not available for any dichloropropane or dichloropropene in any fresh or saltwater species. Based on octanol/water coefficients of dichloropropanes and dichloropropenes, the U.S. EPA. (1979) has estimated the bioconcentration factors for these compounds to range between 10 and 35.

VI. Other Pertinent Information

In the non-aquatic environment, movement of 1,2-dichloropropane in the soil results from diffusion in the vapor phase, as these compounds tend to establish an equilibrium between the vapor phase, water and absorbing phases (Leistra, 1970). 1,2-dichloropropane appears to undergo minimal degradation in soil with the major route of dissipation appearing to be volatilization (Roberts and Staydin, 1976).

Following field application, movement of 1,3-dichloropropene in soil results in vapor-phase diffusion (Leistra, 1970). The distribution of 1,3-dichloropropene within soils depends on soil conditions. For example, cis-1,3-dichlorobenzene is chemically hydrolyzed in moist soils to the corresponding cis-

3-chloroalkyl alcohol, which can be microbially degraded to carbon dioxide and water by Pseudomonas sp. (Van Dijk, 1974).

VII. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria may be changed.

A. Human

The TLV for dichloropropane is 75 ppm (350 mg/m^3) (Am. Conf. Gov. Ind. Hyg., 1977). The draft water criterion (U.S. EPA, 1979) for dichloropropane is 203 µg/l. The draft water criterion for dichloropropenes is 0.63 µg/l (U.S. EPA, 1979).

B. Aquatic

The draft criteria for the dichloropropanes and dichloropropenes to protect freshwater aquatic life are as follows (U.S. EPA, 1979):

Compound	24-Hour Average	Concentration not to be exceeded at any time
1,1-dichloropropane	410 µg/l	930 µg/l
1,2-dichloropropane	920 µg/l	2,100 µg/l
1,3-dichloropropane	4,800 µg/l	11,000 µg/l
1,3-dichloropropene	18 µg/l	250 µg/l

The draft criteria to protect saltwater species are as follows (U.S. EPA, 1979):

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Compound	24-Hour Average	Concentration not to be exceeded at any time
1,1-dichloropropane	not derived	not derived
1,2-dichloropropane	400 µg/l	910 µg/l
1,3-dichloropropane	79 µg/l	180 µg/l
1,3-dichloropropene	5.5 µg/l	14 µg/l

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DICHLOROPROPANES/DICHLOROPROPENES

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No. 80

Dichloropropanol

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

DICHLOROPROPANOL

Summary

There was no evidence found in the available literature to indicate that exposure to dichloropropanol produces carcinogenic effects. Conclusive evidence of mutagenic, teratogenic, or chronic effects of dichloropropanol was not found in the available literature. Acute exposure results in toxicity similar to that induced by carbon tetrachloride, including hepato- and nephrotoxicity. Data concerning the effects of dichloropropanol to aquatic organisms was not found in the available literature.

I. INTRODUCTION

This profile is based on computerized searches of Toxline, Biosis, and Chemical Abstracts, and review of other appropriate information sources as available. Dichloropropanol (molecular weight 128.9), a colorless, viscous liquid with a chloroform-like odor, refers to four isomers with the molecular formula $C_3H_6OCl_2$. The physical properties of each isomer are given below.

	Boiling Point	Density	Solubility (Weast, 1976)		
			Water	Alcohol	Ether
2,3-Dichloro-1-propanol	182°C	1.368	slight	miscible	miscible
1,3-Dichloro-2-propanol	174°C	1.367	very	very	miscible
3,3-Dichloro-1-propanol	82-83°C	1.316	not listed		
1,1-Dichloro-2-propanol	146-148°C	1.3334	slight	very	very

Additional physical data and synonyms of the above isomers are available in Heilbron (1965), Fairchild (1979), Sax (1979), Windholz (1976), and Verschueren (1977).

Dichloropropanol is prepared from glycerol, acetic acid, and hydrogen chloride. It is used as a solvent for hard resins and nitrocellulose, in the manufacture of photographic and Zapon lacquer, as a cement for celluloid, and as a binder for water colors (Windholz, 1976). The compound is considered to be a moderate fire hazard when exposed to heat, flame, or oxidizers, and a disaster hazard in that it may decompose at high temperatures to phosgene gas (Sax, 1979).

II. EXPOSURE

Dichloropropanol was detectable in the air of a glycerol manufacturing plant in the U.S.S.R. (Lipina and Belyakov, 1975). Unreacted dichloropropanol was also found in the wastewater effluent of a halohydrin manufacturing plant (Aoki and Katsube, 1975). No monitoring data are available to indicate ambient air or water levels of the compound.

Human exposure to dichloropropanol from foods cannot be assessed, due to a lack of monitoring data.

Bioaccumulation data on dichloropropanol was not found in the available literature.

III. PHARMACOKINETICS

Pertinent data could not be located in the available literature on the metabolism, distribution, absorption, or excretion of dichloropropanol.

IV. EFFECTS

A. Carcinogenicity

Pertinent data could not be located in the available literature.

B. Mutagenicity

2,3-Dichloropropanol and 1,3-dichloropropanol were evaluated for mutagenicity by a modified Ames assay using S. typhimurium strains. Some evidence of mutagenic activity was seen, but the authors felt that further evidence and clarification of the metabolic activation pathway to mutagens via halcalkanols were necessary (Nakamura, et al. 1979).

C. Teratogenicity, Other Reproductive Effects and Chronic Toxicity

Pertinent data could not be located in the available literature.

D. Acute Toxicity

2,3-Dichloropropanol was found to have an oral LD_{50} in the rat of 90 mg/kg. The lowest published lethal concentration (LC_{LO}) in rats is 500 ppm by inhalation for 4 hours. A dose of 6,800 ug in the eye of the rabbit caused severe irritation (Fairchild, 1979). 1,3-Dichloropropanol was found to have an oral LD_{50} in the rat of 490 mg/kg and lowest published lethal concentration for inhalation exposure in rats of 125 ppm/4 hrs. Ten mg applied to the skin of the rabbit for 24 hours produced mild irritation, and 800 mg/kg was the LD_{50} for the same route and species (Fairchild, 1979).

Several references report the clinical indications of acute dichloropropanol intoxication as being similar to carbon tetrachloride poisoning, i.e., central nervous depression; hepatotoxicity, including hepatic cell necrosis and fatty infiltration; and renal toxicity, including fatty degeneration and necrosis of the renal tubular epithelium (Sax, 1979; Gosselin, et al. 1976).

V. AQUATIC TOXICITY

Data concerning the effects of dichloropropanol to aquatic organisms were not found in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The maximum allowable concentration of dichloropropanol in the working environment air in the U.S.S.R. is 5 mg/m^3 (Lipina and Belyakov, 1975).

The maximum allowable concentration in Class I waters for the production of drinking water is 1 mg/l (Verschueren, 1977).

B. Aquatic

The organoleptic limit in water set in the U.S.S.R. (1970) is 1.0 mg/l (Verschueren, 1977).

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No. 81

1,3-Dichloropropene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

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1,3-DICHLOROPROPENE

SUMMARY

The major environmental source of dichloropropenes is from the use of a mixture of dichloropropenes and dichloropropanes as a soil fumigant. On chronic exposure of rats to dichloropropene mild kidney damage was observed. Dichloropropene has produced subcutaneous tumors at the site of injection, and has been shown to be mutagenic in bacteria. However, not enough information is available to classify this compound as a carcinogen.

The bluegill (Lepomis macrochirus) has a reported 96-hr LC_{50} value of 6060 µg/l; Daphnia magna has a reported 48-hr LC_{50} of 6150 µg/l. For the saltwater invertebrate, Mysidopsis bahia, a reported 96-hr LC_{50} value is 790 µg/l. In the only long-term study available, the value obtained for 1,3-dichloropropene toxicity to fathead minnows (Pimephales promeles) in an embryo-larval test is 122 µg/l. Based on chlorophyll a concentrations and cell numbers, the 96-hr EC_{50} values for the freshwater alga Selenastrum capricornutum are 4,950 and 4,960 µg/l, respectively; for the marine alga Skeletonema costatum, the respective values are 1,000 and 1,040 µg/l.

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1,3-DICHLOROPROPENE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Dichloropropanes/Dichloropropenes (U.S. EPA, 1979a).

1,3-dichloropropene (molecular weight 110.97) is a liquid at environmental temperatures. The isomers of 1,3-dichloropropene have boiling points of 104.3°C for the trans-isomer and 112°C for the cis-isomer, and the densities are 1.217 and 1.224 g/ml, respectively. The water solubility for the two isomers is approximately 0.275 percent. When heated to decomposition temperatures, 1,3-dichloropropene gives off toxic fumes of chlorides (Sax, 1975). Mixtures of cis- and trans- 1,3-dichloropropene and 1,2-dichloropropane are used as soil fumigants. In this document, dichloropropene will refer to either cis- or trans-1,3-dichloropropene. For more information regarding the dichloropropenes, the reader is referred to the EPA/ECAO Hazard Profile on Dichloropropanes/Dichloropropenes (U.S. EPA, 1979b).

II. EXPOSURE

A. Water

Dichloropropene can enter the aquatic environment in the discharges from industrial and manufacturing processes, in run-off from agricultural land, or from municipal effluents. This compound has been identified but not quantified in New Orleans drinking water (Dowty, et al. 1975).

B. Food

Information was found in the available literature concerning the concentration of dichloropropene in commercial foodstuffs. Thus, the amount of this compound ingested by humans is not known. The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor (BCF) of dichloropropene to be 2.9 for the edible portions of fish and shellfish consumed by

Americans. This estimate is based on the octanol/water partition coefficient of dichloropropene.

C. Inhalation

Atmospheric levels of dichloropropene have not been measured. However, it is estimated that about 8 percent of the dichloropropene which is applied to the soil as a fumigant is released to the atmosphere (U.S. EPA, 1979a).

III. PHARMACOKINETICS

A. Absorption

Data on the absorption, distribution and metabolism of dichloropropene could not be located in the available literature.

Data on the excretion of dichloropropene by humans could not be located in the available literature. In the rat, however, approximately 80 percent of an orally administered dose of dichloropropene was eliminated in the urine within 24 hours (Hutson, et al. 1971).

IV. EFFECTS

A. Carcinogenicity

Van Duuren, et al. (1979) investigated the ability of dichloropropene to act as a tumor initiator or promoter in mouse skin, or to cause tumors after subcutaneous injection. Dichloropropene showed no initiation or promotion activity, and only local sarcomas developed in mice following subcutaneous administration. In none of the studies were treatment-related remote tumors observed.

B. Mutagenicity

DeLorenzo, et al. (1977) and Neudecker, et al. (1977) reported that dichloropropene was mutagenic in S. typhimurium strains TA1535 and TA100 but not in TA1978, TA1537, or TA98. Results did not differ with or without the

addition of liver microsomal fraction. Neudecker, et al. (1977) found the cis-isomer to be twice as reactive as the trans-isomer.

C. Teratogenicity and Other Reproductive Effects

No pertinent information regarding the teratogenicity and other reproductive effects could not be located in the available literature.

D. Chronic Toxicity

On exposure of rats to 3 ppm dichloropropene for period of 0.5, 1, 2 or 4 hours/day, 5 days a week for 6 months (Torkelson and Oyen, 1977), or rats, guinea pigs, and rabbits to 1 or 3 ppm of dichloropropene, 7 hours per day for 125-130 days over a 180-day period, only rats exposed 4 hours/day at 3.0 ppm showed an effect (U.S. EPA, 1979a). The only effect observed was a cloudy swelling of the renal tubular epithelium which disappeared by 3 months after exposures ended.

V. AQUATIC TOXICITY

A. Acute Toxicity

Tests on the bluegill, Lepomis macrochirus, yielded a 96-hr LC_{50} value of 6060 µg/l for 1,3-dichloropropene exposure. For Daphnia magna, the 48-hr LC_{50} value is 6,150 µg/l (U.S. EPA, 1978). The observed 96-hr LC_{50} for the saltwater myrid shrimp, Mysidopsis bania, is 790 µg/l (U.S. EPA, 1978).

B. Chronic Toxicity

An embryo-larval test has been conducted with the fathead minnow (Pimephales promeles) and 1,3-dichloropropene. The observed chronic value was 122 µg/l (U.S. EPA, 1979a).

C. Plant Effects

Based on chlorophyll a concentrations and cell numbers, the 96-hr EC_{50} values for the freshwater alga, Selenestrum capricornutum, are 4,950

and 4,960 µg/l, respectively (U.S. EPA, 1978). The respective values for the saltwater alga Skeletonema costatum were 1,000 and 1,040 µg/l (U.S. EPA, 1978).

D. Residues

Measured steady-state bioconcentration factors (BCF) are not available for 1,3-dichloropropene. A BCF of 19 has been estimated based on the octonol/water coefficient for 1,3-dichloropropene (U.S. EPA, 1979a).

E. Other Relevant Information

Following field application, movement of 1,3-dichloropropene in soil results in vapor-phase diffusion (Leistra, 1970). The distribution of 1,3-dichloropropene within soils depends on soil conditions. For example, cis-1,3-dichloropropane is chemically hydrolyzed in moist soils to the corresponding cis-3-chloroalkyl alcohol, which can be microbially degraded to carbon dioxide and water by Pseudomonas sp. (Van Dijk 1974).

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

The draft water criterion for 1,3-dichloropropene is 0.63 µg/l (U.S. EPA, 1979a).

B. Aquatic

The draft criterion to protect freshwater species is 18 µg/l as a 24-hr average not to exceed 250 µg/l at any time. For marine species, the value is 5.5 µg/l as a 24-hr average not to exceed 14 µg/l at any time (U.S. EPA, 1979).

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1,3-DICHLOROPROPENE

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No. 82

Dieldrin

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated dieldrin and has found sufficient evidence to indicate that this compound is carcinogenic.

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DIELDRIN

SUMMARY

Dieldrin is a compound belonging to the group of cyclodiene insecticides. The chronic toxicity of low doses of dieldrin includes shortened life span, liver changes and teratogenic effects. The induction of hepatocellular carcinoma in mice by dieldrin leads to the conclusion that it is likely to be a human carcinogen. Dieldrin has been found to be non-mutagenic in several test systems. The WHO's acceptable daily intake for dieldrin is 0.0001 mg/kg/day.

The toxicity of dieldrin to aquatic organisms has been investigated in numerous studies. The 96-hour LC_{50} values for the common freshwater fish range from 1.1 to 360 µg/l. The acute toxicity is considerably more varied for freshwater invertebrates, with 96-hour LC_{50} values ranging from 0.5 µg/l for the stonefly to 740 µg/l for the crayfish. Acute LC_{50} values for eight saltwater fish species range from 0.66 to 24.0 µg/l in flow-through tests; LC_{50} values for estuarine invertebrates range from 0.70 to 240 µg/l. The only reported chronic values are 0.11 µg/l for steel head trout (Salmo guirdnes) in an embryolarval study and 0.4 µg/l for the guppy (Poecilia reticulata) in a life-cycle test. Both fresh and salt water algae are less sensitive to dieldrin toxicity than the corresponding fish and invertebrates. Bioconcentration factors were 128 for a freshwater alga, 1395 for Daphnia magna, 2993 for the channel catfish, and 8000 for the edible tissues of the Eastern oyster.

DIELDRIN

I. INTRODUCTION

This profile is based on the draft Ambient Water Quality Criteria Document for Aldrin and Dieldrin (U.S. EPA, 1979). Dieldrin is a white crystalline substance with a melting point of 176-177°C and is soluble in organic solvents (U.S. EPA, 1979). The chemical name for dieldrin is 1,2,3,4,10,10-hexachlor-6,7-epoxy-1,4,4a,5,6,7,8,8a-octohydro-endo, exo-1,4:5,8-dimethanonaphthalene.

Dieldrin is extremely stable and persistant in the environment. Its persistance is due to its extremely low volatility (1.78×10^{-7} mm Hg at 20°C) and low solubility in water (186 µg/l at 25-29°C). The time required for 95 percent of the dieldrin to disappear from soil has been estimated to vary from 5 to 25 years depending on the microbial flora of the soil (Edwards, 1966). Patil, et al. (1972) reported that dieldrin was not degraded or metabolized in sea water or polluted water.

Dieldrin was primarily used as a broad spectrum insecticide until 1974, when the U.S. EPA restricted its use to termite control by direct soil injection, and non-food seed and plant treatment (U.S. EPA, 1979). From 1966 to 1970, the amount of dieldrin used in the United States decreased from 500 to approximately 335,000 tons (U.S. EPA, 1979). This decrease in use has been attributed primarily to increased insect resistance to dieldrin and to development of substitute materials. Although the production of dieldrin is restricted in the United States, formulated products containing dieldrin are imported from Europe (U.S. EPA, 1979).

II. EXPOSURE

A. Water

Dieldrin has been applied to vast areas of agricultural land and aquatic areas in the United States, and in most parts of the world. As a result, this pesticide is found in most fresh and marine waters. Dieldrin has been measured in many freshwaters of the United States, with mean concentrations ranging from 5 to 395 ng/l in surface water and from 1 to 7 ng/l in drinking water (Epstein, 1976). Levels as high as 50 ng/l have been found in drinking water (Harris, et al. 1977). The half-life of dieldrin in water, 1 meter in depth, has been estimated to be 723 days (MacKay and Wolkoff, 1973).

B. Food

Dieldrin is one of the most stable and persistant organochlorine pesticides (Nash and Woolson, 1967), and because it is lipophilic, it accumulates in the food chain (Wurster, 1971). Its persistance in soil varies with the type of soil. (Matsumura and Boush, 1967).

The U.S. EPA (1971) estimated that 99.5 percent of all human beings have dieldrin residues in their tissue. These residues are primarily due to contamination of foods of animal origin. The overall concentration of dieldrin in the diet in the United States has been calculated to be approximately 43 ng/g of food consumed (Epstein, 1976). The U.S. EPA has estimated the weighted average bioconcentration factor for dieldrin to be 4,500 in the edible portion of fish and shellfish consumed by Americans (U.S. EPA, 1979). This estimate is based on measured

steady-state bioconcentration studies in several species of fish and shellfish.

C. Inhalation

Dieldrin enters the air through various mechanisms, such as spraying, wind action, water evaporation, and adhesion to particulates. The U.S. EPA detected dieldrin in more than 85 percent of the air samples tested between 1970-1972, with the mean levels ranging from 1 to 2.8 ng/m^3 (Epstein, 1976). From these levels, the average daily intake of dieldrin by respiration was calculated to be 0.035 to 0.098 µg.

Although dieldrin is no longer used in the United States, there is still the possibility of airborne contamination from other parts of the world.

D. Dermal

Dermal exposure to dieldrin is limited to those involved in its manufacture or application as a pesticide. Wolfe, et al. (1972) reported that exposure in workers was mainly through dermal absorption rather than inhalation. The ban on the manufacture of dieldrin in the United States has greatly reduced the risk of exposure.

III. PHARMACOKINETICS

A. Absorption

The absorption of dieldrin by the upper gastrointestinal tract begins almost immediately after oral administration in rats and has been found to vary with the amount of solvent used (Heath and Vandekar, 1964). These authors also demonstrated that absorption takes place via the portal vein, and that dieldrin

could be recovered from the stomach, small intestine, large intestine and feces one hour after oral administration.

B. Distribution

The distribution of dieldrin has been studied in numerous feeding experiments. Dieldrin has an affinity for fat, but high concentrations are also reported in the liver and kidney, with moderate concentrations in the brain one and two hours after administration in rats (Heath and Vandekar, 1964). Deichman, et al. (1968) fed dieldrin to rats for a period of 183 days. The mean concentration in the fat was 474 times that in the blood, while the concentration in the liver was approximately 29 times the blood concentration.

Additional animal studies on the distribution of dieldrin have shown that concentrations in tissues are dose related and may vary with the sex of the animal (Walker, et al. 1969). Matthews, et al. (1971) found that female rats administered oral doses of dieldrin had higher tissue levels of the compound than male rats. The females stored the compound predominatly as dieldrin. In males, other metabolites, identified as keto-dieldrin trans-hydro-aldrin and a polar metabolite, were detected.

The concentrations of dieldrin in human body fat were found to be 0.15 $\pm$ 0.02 µg/g for the general population and 0.36 µg/g in one individual exposed to aldrin (aldrin is metabolized to dieldrin) (Dale and Quinby, 1963). The mean concentrations of dieldrin in the fat, urine, and plasma of pesticide workers were 5.67, 0.242 and 0.0185 mg/g, respectively (Hayes and Curley, 1968). Correlations between the dose and length of exposure to dieldrin and the concentration of dieldrin in the blood and

other tissues have been reported (Hunter, et al. 1969). Dieldrin residues in the blood plasma of workers averaged approximately four times higher than that in the erythrocytes (Mick, et al. 1971).

C. Metabolism

The epoxidation of aldrin to dieldrin has been reported in many organisms, including man (U.S. EPA, 1979). The reaction is NADPH-dependent, and the enzymes have been found to be heat labile (Wong and Terriere, 1965).

The metabolism of dieldrin has been studied in several species, including mice, rats, rabbits, and sheep. Dieldrin metabolites have been identified in the urine and feces in the form of several compounds more polar than the parent compound (U.S. EPA, 1979). Bedford and Hutson (1976) summarized the four known metabolic products of dieldrin in rodents as 6,7-trans-dihydroxy-dihydro-aldrin (trans-diol) and tri-cyclic dicarboxylic acid (both of which are products of the transformation of the epoxy group), the syn-12-hydroxy-dieldrin (a mono-hydro derivative), and the pentachloroketone. Male rats have been found to metabolize dieldrin more rapidly than females (U.S. EPA, 1979), and differences in the metabolism of dieldrin have been found between species (Baldwin, et al. 1972).

D. Excretion

Dieldrin is excreted mainly in the feces and, to some extent, in the urine in the form of several polar metabolites (U.S. EPA, 1979). However, rabbits fed ^{14}C-dieldrin over a 21 week period excreted 42 percent of the radioactivity by the end of 22 weeks, with 2 to 3 times as much excreted in the urine

as in the feces. Robinson, et al. (1969) found that 99 percent of the dieldrin fed to rats for 8 weeks was excreted during a subsequent 90-day observation period. The half-life of dieldrin in the liver and blood was 1.3 days for the period of rapid elimination and 10.2 days for a later, slower period. The half-life of dieldrin in adipose tissue and brain were 10.3 and 3.0 days, respectively.

The concentration of dieldrin in the urine of the general human population is 0.8 mg/l for man and 1.3 mg/l for women as compared to 5.3, 13.8, or 51.4 mg/l for men with low, medium, or high exposure (Ceuto and Biros, 1967). The half-life for dieldrin in the blood of humans ranges from 141-592 days with a mean of 369 days (Hunter, et al. 1969). Jager (1970) reported the half-life to be 266 days. Because there is a relationship between the concentration of dieldrin in the blood and that in adipose and other tissues, it seems likely that the half-life in the blood may reflect the over-all half-life in other tissues (U.S. EPA, 1979).

IV EFFECTS

A. Carcinogenicity

Dieldrin has produced liver tumors in several strains of mice according to six reports of chronic feeding studies (NCI, 1976 (43 FR 2450); Davis and Fitzhugh, 1962; Davis, 1965; Song and Harville, 1964; Walker, et al. 1972; Thorpe and Walker, 1973). In rats, dieldrin has failed to induce a statistically significant excess of tumors at any site in three strains during six chronic feeding studies (Treon and Cleveland, 1965; Cleveland, 1966;

Fitzhugh, et al. 1964; Deichman, et al. 1967; Walker, et al. 1969; Deichmann, et al. 1970).

The only information concerning the carcinogenic potential of dieldrin in man is an occupational study by Versteeg and Jager (1973). The workers had been employed in a plant producing aldrin and dieldrin with a mean exposure time of 6.6 years. An average of 7.4 years had elapsed since the end of exposure. No permanent adverse effects, including cancer, were observed.

B. Mutagenicity

Microbial assays concerning the mutagenicity of aldrin and dieldrin have yielded negative results even when some type of activation system was added (Fahrig, 1973; Bidwell, et al. 1975; Marshall, et al. 1976). A host-mediated assay and a dominant lethal test, also yielded negative results (Bidwell, et al. 1975). Majumdar, et al. (1977), however, found dieldrin to be mutagenic in S. typhiphimurium, although these positive results were questioned because several differences existed between their procedures and those recommended (U.S. EPA, 1979).

A decrease in the mitotic index was observed in vivo with mouse bone marrow cells and in vitro with human lung cells treated with 1 mg/kg and 1 µg/ml dieldrin, respectively (Majumdar, et al. 1976).

D. Teratogenicity

In 1967, Hathaway, et al. established that ^{14}C-dieldrin could cross the placenta in rabbits. Dieldrin caused significant increases in fetal death in hamsters, and increased fetal anomalies (i.e. open eye, webbed foot, cleft palate, and others)

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in hamsters and mice when administered in single oral doses during gestation (hamsters 50, 30, 5 mg/kg and mice 25, 15, 2.5 mg/kg) (Ottolenghi, et al. 1974).

However, in subsequent studies no evidence has been found that dieldrin causes teratogenic effects in mice and rats (Chernoff, et al. 1975) or mice (Dix, et al. 1977).

D. Other Reproductive Effects

Deichmann (1972) reported that aldrin and dieldrin (25 mg/kg/diet) fed to mice for six generations affected fertility, gestation, viability, lactation, and survival of the young. However, no changes in weight or survival of fetuses were found in mice administered dieldrin for day 6 through 14 of gestation at doses already mentioned in this report (Ottolenghi, et al. 1974).

E. Chronic Toxicity

The other effects produced by chronic administration of dieldrin to mice, rats, and dogs include shortened life span, increased liver to body weight ratio, various changes in liver histology, and the induction of hepatic enzymes (U.S. EPA, 1979).

F. Other Relevant Information

Since aldrin and dieldrin are metabolized by way of the mixed function oxidase (MFO) system and dieldrin has been found to induce the production of these enzymes, any inducer or inhibitor of the MFO enzymes should affect the metabolism of dieldrin (U.S. EPA, 1979). Dieldrin fed in low doses prior to an acute dose of dieldrin alters its metabolism (Baldwin, et al. 1972). Dieldrin can effect the storage of DDT (U.S. EPA,

1979) and induce a greater number of tumors in mice when administered with DDT as compared to DDT alone (Walker, et al. 1972).

V. AQUATIC TOXICITY

A. Acute Toxicity

The acute toxicity of dieldrin has been investigated in numerous studies. Reported 96-hour LC_{50} values for freshwater fish are 1.1 to 9.9 µg/l for rainbow trout, Salmo gairdneri (Katz, 1961; Macek, et al. 1969); 16 to 36 µg/l for fathead minnows, Pimephales promelas (Henderson, et al. 1959; Tarzwell and Henderson, 1957); and 8 to 32 µg/l for the bluegill, Lepomis macrochirus (Henderson, et al. 1959; Macek, et al. 1969; Tarzwell and Henderson, 1957). Freshwater invertebrates appear to be more variable in their sensitivity to acute dieldrin toxicity. The 96-hour LC_{50} values range from 0.5 µg/l for the stone fly (Sanders and Cope, 1968) to 740 µg/l for the crayfish (Sanders, 1972).

The acute LC_{50} values for eight saltwater fish species range from 0.66 to 24.0 µg/l in flow-through tests (Butler, 1963; Earnest and Benville, 1972; Korn and Earnest, 1974; Parrish, et al. 1973; Schoettger, 1970; and Lowe, undated). LC_{50} values ranging from 0.7 to 240.0 µg/l have been reported for estuarian invertebrates species, with the most sensitive species tested being the commercially important pink shrimp, Penaeus duorarum (U.S. EPA, 1978).

B. Chronic Toxicity

Chronic toxicity has been studied in two species of freshwater fish. The chronic value for steelhead trout (Salmo gairdneri) from an embro-larval study is 0.11 µg/l (Chadwick

and Shumway, 1969). For the guppy, Poecilia reticulata, in a life-cycle test, the chronic value is 0.4 µg/l (Roelofs, 1971).

C. Plant Effects

Freshwater plants are less sensitive to dieldrin than freshwater fish or invertebrates. For example, a concentration of 100 µg/l caused a 22 percent reduction in the biomass of the alga Scenedlesmus quadricaudata (Stadnyk and Campbell, 1971), and 12,800 µg/l reduced growth by 50 percent in the diatom, Navicula seminulum after 5 days of exposure (Cairns, 1968). In a saltwater plant species growth rate was reduced at concentrations of approximately 950 µg/l (Batterton, et al. 1971).

D. Residues

Bioconcentration factors (BCF) have been determined for 9 freshwater species (U.S. EPA, 1978). Representative BCF values are 128 for the alga, Scenedesmus obliguus (Reinert, 1972, 1395 for Daphnia magna (Reinert, 1972), 2385-2993 for the channel catfish, Ictalurus punctatus (Shannon, 1977a; 1977b) and 68,268 for the yearling lake trout, Salvelinus namaycush (Reinert, et al. 1974). The edible tissue of the Eastern oyster, Crassostrea virginica, had a BCF value of 8000 after 392 days of exposure (Parrish, 1974). Spot, Leiostomus xanthurus, had a BCF of 2,300 after 35 days exposure to dieldrin (Parrish, et al. 1973).

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

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A. Human

The current exposure level for dieldrin set by OSHA is an air time-weighted average of 250 $\mu g/m^3$ for skin absorption (37 FR 22139). In 1969, the U.S. Public Health Service Advisory Committee recommended that the drinking water standard for dieldrin be 17 µg/l (Mrak, 1969). The U.N. Food and Agricultural Organization/World Health Organization's acceptable daily intake for dieldrin is 0.0001 mg/kg/day (Mrak, 1969).

The carcinogenicity data of Walker, et al. (1972) were used to calculate the draft ambient water quality criterion for dieldrin of 4.4×10^{-2} ng/l (U.S. EPA, 1979). This level keeps the lifetime cancer risk for humans below 10^{-5}.

B. Aquatic

The draft criterion to protect freshwater life is 0.0019 µg/l as a 24-hour average; the concentration should not exceed 1.2 µg at any time. To protect saltwater aquatic life, the draft criterion is 0.0069 µg/l as a 24-hour average; the concentration should not exceed 0.16 µg/l at any time.

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No. 83

o,o-Diethyl Dithiophosphoric Acid

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

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o,o-DIETHYL DITHIOPHOSPORIC ACID

Summary

There is no available information to indicate that o,o-diethyl dithiophosphoric acid produces carcinogenic, mutagenic, teratogenic, or adverse reproductive effects.

A possible metabolite of the compound, o,o-diethyl dithiophosphoric acid, did not show mutagenic activity in Drosophila, E. coli, or Saccharomyces.

The pesticide phorate, which may release o,o-diethyl dithiophosphoric acid as a metabolite, has shown some teratogenic effects in developing chick embryos and adverse reproductive effects in mice.

An acute value of 47.2 µg/l has been reported for rainbow trout exposed to a diethyl dithiophosphoric acid analogue, dioxathion. A synergistic toxic effect with the latter chemical and malathion is suggested.

I. INTRODUCTION

o,o-Diethyl hydrogen dithiophosphate, CAS registry number 298-06-6, also called o,o-diethyl phosphorodithioic acid or o,o-diethyl dithiophosphoric acid, is used primarily as an intermediate in the synthesis of several pesticides: azinphosmethyl, carbophenothion, dialifor, dioxathion, disulfoton, ethion, phorate, phosalone and terbufos. It is made from phosphorus pentasulfide (SRI, 1976).

II. EXPOSURE

A. Water

Pertinent data were not found in the available literature; however, if found in water, its presence would most likely be due to microbial action on phorate or disulfoton (Daughton, et al. 1979), or as a contaminant of any of the above pesticides for which it is a starting compound.

B. Food

Pertinent data were not found in the available literature; however, if present in food, the compound would probably originate from the same sources discussed above. Orgarophosphorus pesticide residues have been found in food (Vettorazzi, 1976).

C. Inhalation

Pertinent data were not found in the available literature; however, major exposure could come from fugitive emissions in manufacturing facilities.

D. Dermal

Pertinent data were not found in the available literature.

III. PHARMACOKINETICS

A. Absorption

Information relating specifically to the absorption of o,o-diethyl dithophosphoic acid was not found in the available literature. Acute toxicity studies with the pesticides disulfoton and phorate indicate that these related organophosophorous compounds are absorbed following oral or dermal administration (Gaines, 1969).

B. Distribution

Pertinent data were not found in the available literature. Oral administration of labelled phorate, the S-(ethyl thio)methyl derivative of o,o-diethyl dithiophosphoric acid, to cows accumulated in liver, kidney, lung, alimentary tract, and glandular tissues; fat samples showed very low residues (Bowman and Casida, 1958).

C. Metabolism

Pertinent data were not found in the available literature. Metabolism studies with disulfoton (Bull, 1965) and phorate (Bowman and Casida, 1958) indicate that both compounds are converted to diethyl phosphorodithioate, diethyl phorphorothioate, and diethyl phosphate.

D. Excretion

Pertinent data were not found in the available literature. Based on animal studies with related organophosphorous compounds, the parent compound and its oxidative metabolites may be expected to eliminated primarily in the urine (Matsumura, 1975).

IV. EFFECTS

A. Carcinogenesis

The dioxane s-s diester with o,o-diethyl dithiophosphoric acid, dioxathion, has been tested for carcinogenicity in mice and rats by

long-term feeding. No carcinogenic effects were noted in either species (NCI, 1978).

B. Mutagenicity

Diethyl phosphorothioate, a possible metabolite of the parent compound, did not show mutagenic activity in Drosophila, E. coli, or Saccharomyces (Fahrig, 1974).

C. Teratogenicity

Pertinent data were not found in the available literature. Injection of phorate into developing chick embryos has been reported to produce malformations (Richert and Prahlad, 1972).

D. Other Reproductive Effects

Pertinent data were not found in the available literature. An oral feeding study conducted in mice with phorate (0.6 to 3.0 ppm) indicated that the highest level of compound did produce some adverse reproductive effects (American Cyanamid, 1966). Chronic feeding of mice with technical dioxathion at levels of 450 to 600 ppm produced some testicular atrophy (NCI, 1978).

E. Chronic Toxicity

Chronic feeding of technical dioxathion produced hyperplastic nodules in livers of male mice. o,o-Diethyl dithiophosphoric acid, like other organophosphates, is expected to produce cholinesterase inhibition (NAS, 1977).

V. AQUATIC TOXICITY

A. Acute

Marking (1977) reports on LC_{50} value of 47.2 µg/l for rainbow trout (Salmo gairdneri) exposed to the dithiodioxane analogue • of bis(o,o-diethyl dithiophosphoric acid), dioxathion, and an LC_{50} value of

3.44 µg/l when this latter compound is applied in combination with malathion. The synergistic action with malathion suggests that the combination is more than eight times as toxic as either of the individual chemicals.

B. Chronic, Plant Effects, and Residues.

Pertinent data were not found in the available literature.

VI. EXISTING GUIDELINES

Existing guidelines or standards were not found in the available literature.

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No. 84

O,O-Diethyl-S-methyl Phosphorodithioate

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

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o,o-DIETHYL-S-METHYL PHOSPHORODITHIOATE

Summary

There is no available information on the possible carcinogenic, mutagenic, teratogenic or adverse reproductive effects of o,o-diethyl-S-methyl phosphorodithioate. Pesticides containing the o,o-diethyl phosphorodithioate moiety did not show carcinogenic effects in rodents (dioxathion) or teratogenic effects in chick embryos (phorate). The possible metabolite of this compound, o,o-diethyl phosphorothioate, did not show mutagenic activity in Drosophila, E. coli, or Saccharomyces. o,o-Diethyl-S-methyl phosphorodithioate, like other organophosphate compounds, is expected to produce cholinesterase inhibition in humans.

There is no available data on the aquatic toxicity of this compound.

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o,o-DIETHYL-S-METHYL PHOSPHORODITHIOATE

I. INTRODUCTION

o,o-Diethyl-S-methyl phosphorodithioate (CAS registry number 3288-58-2) is described in German patents 1,768,141 (CA 77:151461s) and 1,233,390 (CA 66:115324o). The latter states the compound has "partly insecticidal, acaricidal and fungicidal activity" and is useful as an intermediate for organic synthesis. It has the following physical and chemical properties:

Formula:	C_5H_{13}
Molecular Weight:	200
Boiling Point: (CA 55:8335h)	100°C to 102°C (4 torr)
Density: (CA 55:8335h)	1.192420

Pertinent data were not found in the available literature with respect to production, consumption or the current use of this compound.

II. EXPOSURE

Pertinent data were not found in the available literature.

III. PHARMACOKINETICS

A. Absorption

Information relating specifically to the absorption of o,o-diethyl-S-methyl phosphorodithioate was not found in the available literature. Oral administration of the S-ethylthio derivative of this compound, the insecticide phorate, indicates that this derivative is absorbed from the gastrointestinal tract (Bowman and Casida, 1958).

B. Distribution

Pertinent data were not found in the available literature. Studies with ^{32}P radiolabelled phorate in the cow indicated that following oral administration, residues were found in the liver, kidney, lung,

alimentary tract, and glandular tissues; fat samples showed very low residues (Bowman and Casida, 1958).

C. Metabolism

Pertinent data were not found in the available literature. Based on metabolism studies with various organophosphates in mammals, o,o-diethyl-S-methyl phosphorodithioate may be expected to undergo hydrolysis to diethyl phosphorodithioic acid, diethyl phosphorothioic acid, and diethyl phosphoric acid (Matsumura, 1975).

D. Excretion

Pertinent data were not found in the available literature. Related metabolites (o,o-diethyl phosphorodithioic, phosphorothioic, and phosphoric acids) have been identified in the urine of rats fed phorate (Bowman and Casida, 1958).

IV. EFFECTS

A. Carcinogenicity

Pertinent data were not found in the available literature. The dioxane-S-S-diester with o,o-diethyl phosphorodithioate, dioxathion, has been tested for carcinogenicity in mice and rats by long-term feeding. No carcinogenic effects were noted in either species (NCI, 1978).

B. Mutagenicity

Pertinent data were not found in the available literature. Diethyl phosphorothioate, a possible metabolite of the parent compound, did not show mutagenic activity in Drosphila, E. coli, or Saccharomyces (Fahrig, 1974).

C. Teratogenicity

Pertinent data were not found in the available literature. Injection of phorate into developing chick embryos has been reported to produce malformations (Richert and Prahlad, 1972).

D. Other Reproductive Effects

Pertinent data were not found in the available literature. An oral feeding study conducted in mice with phorate (0.6 to 3.0 ppm) indicated that the highest level of compound did produce some adverse reproductive effects (American Cyanamid, 1966). Chronic feeding of rats with technical dioxathion at levels from 450 to 600 ppm produced some testicular atrophy (NCI, 1978).

E. Chronic Toxicity

Pertinent data were not found in the available literature. Chronic feeding of technical dioxathion produced hyperplastic nodules in the livers of male mice. O,O-Diethyl-S-methyl phosphorodithioate, like other organophosphates, is expected to produce cholinesterase inhibition (NAS, 1977).

V. AQUATIC TOXICITY

Pertinent data were not found in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

Existing guidelines and standards were not found in the available literature.

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References

American Cyanamid. 1966. Toxicity data on 15 percent Thimet granules. Unpublished report. In: Initial Scientific and Minieconomic Review of Phorate (Thimet) Washington, DC: Office of Pesticide Programs.

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No. 85

Diethyl Phthalate

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

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DIETHYL PHTHALATE

SUMMARY

Diethyl phthalate has been shown to produce mutagenic effects in the Ames Salmonella assay.

Teratogenic effects were reported following i.p. administration of diethyl phthalate to pregnant rats. This same study has also indicated fetal toxicity and increased resorptions after i.p. administration of DEP.

Evidence that diethyl phthalate produces carcinogenic effects has not been found.

A single clinical report indicates that the development of hepatitis in several hemodialysis patients may have been related to leaching of diethyl phthalate from the plastic tubings utilized.

Diethyl phthalate appears to be more toxic for marine species acutely tested, with a concentration of 7,590 µg/l being reported as the LC_{50} in marine invertebrates. The data base for the toxic effects of diethyl phthalates to aquatic organisms is insufficient to draft criterion for their protection.

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DIETHYL PHTHALATE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Phthalate Esters (U.S. EPA, 1979a).

Diethyl phthalate (DEP) is a diester of the ortho form of benzene dicarboxylic acid. The compound has a molecular weight of 222.23, specific gravity of 1.123, boiling point of 296.1°C, and is insoluble in water (U.S. EPA, 1979a).

DEP is used as a plasticizer for cellulose ester plastics and as a carrier for perfumes.

The 1977 current production of diethyl phthalate was: 8.75×10^3 tons/year (U.S. EPA, 1979a).

Phthalates have been detected in soil, air, and water samples; in animal and human tissues; and in certain vegetation. Evidence from in vitro studies indicate that certain bacterial flora may be capable of metabolizing phthalates to the monoester form (Engelhardt, et al. 1975).

II. EXPOSURE

Phthalate esters appear in all areas of the environment. Environmental release of the phthalates may occur through leaching of plasticizers from plastics, volatilization of phthalates from plastics, and the incineration of plastic items. Human exposure to phthalates includes contaminated foods and fish, dermal application in cosmetics, and parenteral administration by use of plastic blood bags, tubings, and infusion devices (mainly DEHP release) (U.S. EPA, 1979a).

Monitoring studies have indicated that most water phthalate concentrations are in the ppm range, or 1-2 µg/l (U.S. EPA, 1979a). Industrial air monitoring studies have measured air levels of phthalates from 1.7 to 66 mg/m^3 (Milkov, et al. 1975). Information on levels of DEP in foods is not available. The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor for DEP to be 270 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on measured steady-state bioconcentration studies in bluegills.

III. PHARMACOKINETICS

Specific information is not available on the absorption, metabolism, distribution, or excretion of DEP. The reader is referred to a general coverage of phthalate metabolism in the phthalate ester hazard profile (U.S. EPA, 1979b).

IV. EFFECTS

A. Carcinogenicity

Pertinent information could not be located in the available literature.

B. Mutagenicity

Diethyl phthalate has been shown to produce mutagenic effects in the Ames Salmonella assay (Rubin, et al. 1979).

C. Teratogenicity

Administration of DEP to pregnant rats by i.p. injection has been reported to produce teratogenic effects (Singh, et al. 1972).

D. Other Reproductive Effects

Fetal toxicity and increased resorptions were produced following i.p. injection of pregnant rats with DEP (Singh, et al. 1972).

E. Chronic Toxicity

A single clinical report has been cited by the U.S. EPA (1979a) which correlated leaching of DEP from hemodialysis tubing in several patients with hepatitis. Characterization of all compounds present in the hemodialysis fluids was not done.

V. AQUATIC TOXICITY

A. Acute Toxicity

Among aquatic organisms, the bluegill sunfish, Lepomis macrochirus, has been shown to be acutely sensitive to diethyl phthalate; a 96-hour static LC_{50} of 98,200 µg/l is reported (U.S. EPA, 1978). For the freshwater invertebrate, Daphnia magna, a 48-hour static LC_{50} of 51,100 µg/l was obtained. Marine organisms proved to be more sensitive, with the sheepshead minnow, Cyprinodon variegatus, showing a 96-hour static LC_{50} of 29,600 µg/l, while the mysid shrimp, Mysidopsis bahia, showed an 96-hour static LC_{50} of 7,590 µg/l (U.S. EPA, 1978).

B. Chronic Toxicity

Pertinent information could not be located in the available literature.

C. Plant Effects

Effective concentrations based on chlorophyl a content and cell number for the freshwater alga, Selena-

strum capricornutum, ranged from 85,600 to 90,300 µg/l, while the marine alga, Skeletonema costatum, was more sensitive, with effective concentrations ranging from 65,500 to 85,000 µg/l.

D. Residues

A bioconcentration of 117 was obtained for the freshwater invertebrate, Daphnia magna.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have gone through the process of review; therefore, there is a possibility that these criteria will be changed.

A. Human

Based on "no effect" levels observed in chronic feeding studies with rats or dogs, the U.S. EPA has calculated an acceptable daily intake (ADI) level of 438 mg/day for DEP.

The recommended water quality criterion level for protection of human health is 50 mg/l for DEP (U.S. EPA, 1979a).

B. Aquatic

Data are insufficient to draft criterion for the protection of either freshwater or marine organisms (U.S. EPA, 1979a).

DIETHYL PHTHALATES

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Milkov, L.E., et al. 1975. Health status of workers exposed to phthalate plasticizers in the manufacture of artificial leather and films based on PVC resins. Environ. Health Perspect. Jan. 1975.

Rubin, R.J., et al. 1979. Ames mutagenic assay of a series of phthalic acid esters: Positive response of the dimethyl and diethyl esters in TA 100. Abstract. Soc. Toxicol. Annu. Meet. March 11, 1979, New Orleans.

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U.S. EPA. 1979b. Environmental Criteria and Assessment Office. Hazard Profile: Phthalate Esters (Draft).

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No. 86

Dimethylnitrosamine

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
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APRIL 30, 1980

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DIMETHYLNITROSAMINE

SUMMARY

Dimethylnitrosamine produces liver and kidney tumors in rats. It is mutagenic in several assay systems. No information specifically dealing with the teratogenicity, chronic toxicity or other standard toxicity tests of dimethylnitrosamine was available for review.

Hepatocellular carcinoma has been induced in rainbow trout administered 200 to 800 µg dimethylnitrosamine in their diet.

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DIMETHYLNITROSAMINE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Nitrosamines (U.S. EPA, 1979a).

Specific information on the properties, production, and use of dimethylnitrosamine was not available. For general information on dimethylnitrosamine, refer to the ECAO/EPA Hazard Profile for Nitrosamines (U.S. EPA, 1979b).

Dimethylnitrosamine can exist for extended periods of time in the aquatic environment (Tate and Alexander, 1975; Fine, et al., 1977a).

II. EXPOSURE

A. Water

Dimethylnitrosamine has been detected at a concentration of 3 to 4 µg/l in wastewater samples from waste treatment plants adjacent to, or receiving effluent from, industries using nitrosamines or secondary amines in production operations (Fine, et al., 1977b).

B. Food

Dimethylnitrosamine was found to be present in a variety of foods (including smoked, dried or salted fish, cheese, salami, frankfurters, and cured meats) in the 1 to 10 µ/kg range and occasionally at levels up to 100 µg/kg (Montesano and Bartsch, 1976).

The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor for dimethylnitrosamine for the edible portions of fish and shellfish consumed by

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Americans to be 0.06. This estimate is based on the n-octanol/water partition coefficient of dimethylnitrosamine.

C. Inhalation

Dimethylnitrosamine has been detected in ambient air samples collected near two chemical plants, one using the amine as a raw material and the other discharging it as an unwanted byproduct (Fine, et al., 1977a).

Tobacco smoke contains dimethylnitrosamine. The intake of dimethylnitrosamine from smoking 20 cigarettes per day has been estimated at approximately 2 µg/day (U.S. EPA, 1979a).

III. PHARMACOKINETICS

A. Absorption

Pertinent data could not be located in the available literature.

B. Distribution

Following intravenous injection into rats, dimethylnitrosamine is rapidly and rather uniformly distributed throughout the body (Magee, 1972).

C. Metabolism and Excretion

In vitro studies have demonstrated that the organs in the rat with the major capacity for metabolism of dimethylnitrosamine are the liver and kidney (Montesano and Magee, 1974). After administration of ^{14}C-labeled dimethylnitrosamine to rats or mice, about 60 percent of the isotope appears as $^{14}CO_2$ within 12 hours, while 4 percent is excreted

in the urine (Magee, et al., 1976). Dimethylnitrosamine is excreted in the milk of female rats (Schoental, et al., 1974).

IV. EFFECTS

A. Carcinogenicity

Chronic feeding of dimethylnitrosamine at doses of 50 mg/kg induces liver tumors in rats (Magee and Barnes, 1956; Rajewski, et al., 1966). Shorter, more acute exposures to dimethylnitrosamine ranging from 100 to 200 mg/kg produce kidney tumors in rats and liver tumors in hamsters (Magee and Barnes, 1959; Tomatis and Cafis, 1967). A single unspecified intraperitoneal dose given to newborn mice induced hepatocellular carcinomas (Toth, et al., 1964).

B. Mutagenicity

Dimethylnitrosamine and diethylnitrosamine have been reported to induce forward and reverse mutations in S. typhimurium, E. coli, Neurospora crassa and other organisms; gene recombination and conversion in Saccharomyces cerevisiae; "recessive lethal mutation" in Drosophila; and chromosome aberrations in mammalian cells (Montesano and Bartsch, 1976). Nitrosamines must be metabolically activated to be mutagenic in microbial assays (U.S. EPA, 1979a). Negative results were obtained in the mouse dominant lethal test (U.S. EPA, 1979a).

C. Teratogenicity and Other Reproductive Effects

Pertinent information could not be located in the available literature on the teratogenicity and other reproductive effects of dimethylnitrosamine.

D. Chronic Toxicity

Pertinent information could not be located in the available literature on the chronic activity of dimethylnitrosamines.

E. Other Relevant Information

Aminoacetonitrile, which inhibits the metabolism of dimethylnitrosamine, prevented the toxic and carcinogenic effects of dimethylnitrosamine in rat livers (Magee, et al., 1976).

Ferric oxide, cigarette smoke, volatile acids, aldehydes, methyl nitrite, and benzo(a)pyrene have been suggested to act in a cocarcinogenic manner with dimethylnitro-samine (Stenback, et al., 1973; Magee, et al., 1976).

V. AQUATIC TOXICITY

Pertinent information about acute and chronic aquatic toxicity was not found in the available literature. Additionally, no mention was made in any reports about plant effects or residues.

One study reported that Shasta strain rainbow trout (Salmo gairdneri), fed dimethylnitrosamine in their diet for 52 weeks, developed a dose-response incidence of hepatocellular carcinoma during a range of exposures from 200 to 800 mg dimethylnitrosamine per kg body weight 52 to 78 weeks after dosing (Grieco, 1978).

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have gone

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through the process of public review; therefore, there is a possibility that these criteria may be changed.

A. Human

The U.S. EPA (1979a) has estimated that the water concentrations of dimethylnitrosamine corresponding to lifetime cancer risks for humans of 10^{-5}, 10^{-6}, or 10^{-7} are 0.026 µg/l, 0.0026 µg/l, and 0.00026 µg/l, respectively.

B. Aquatic

Data are insufficient to draft freshwater marine criteria for dimethylnitrosamine.

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No. 87

2,4-Dimethylphenol

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

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2,4-DIMETHYLPHENOL

Summary

2,4-Dimethylphenol (2,4-DMP) is an intermediate in a number of industrial and agricultural products. The main route of exposure for humans is dermal with 2,4-DMP being readily absorbed through the skin.

Little data is available on the mammalian effects of 2,4-DMP. Tests on mice conclude that the compound may be a promoting agent in carcinogenesis. 2,4-DMP inhibits vasoconstriction in isolated rat lungs; this ability may cause adverse health effects in chronically exposed humans.

A reported 96-hour LC_{50} value for fathead minnows is 16,750 µg/l; chronic value using embryo-larval stages of the same species is 1,100 µg/l. Daphnia magna has an observed 48-hour LC_{50} value of 2,120 µg/l. In limited testing, one aquatic alga and duckweed are over 100 times less sensitive than the Daphnia in acute exposures. The bioconcentration factor for 2,4- dimethylphenol is 150 for the bluegill. From half-life studies, residues of the chemical are not a potential hazard for aquatic species.

I. INTRODUCTION

This profile is based primarily on the Ambient Water Quality Criteria Document for 2,4-Dimethylphenol (U.S. EPA, 1979).

2,4-Dimethylphenol (2,4-DMP) is derived from coal and petroleum sources and occurs naturally in some plants. 2,4-DMP ($C_8H_{10}O$) is usually found with the five other dimethylphenol and three methylphenol isomers. It has a molecular weight of 122.17 and normally exists as a colorless crystalline solid. 2,4-DMP has a melting point of 27 to 28°C, a boiling point of 210°C (at 760 mm Hg), a vapor pressure of 1 mm Hg at 52.8°C, and a density of 0.0965 g/ml at 20°C (U.S. EPA, 1979).

2,4-DMP is a weak acid (pk_a-10.6) and is soluble in alkaline solutions. It readily dissolves in organic solvents and is slightly soluble in water (Weast, 1976).

2,4-DMP is a chemical intermediate in the manufacture of a number of industrial and agricultural products, including phenolic antioxidants, disinfectants, solvents, pharmaceuticals, insecticides, fungicides, plasticizers, rubber chemicals, polyphenylene oxide, wetting agents, and dyestuffs. It is also found in lubricants, gasolines, and cresylic acid (U.S. EPA, 1979).

Very little information exists on the environmental persistence of 2,4-DMP. Complete biodegradation of 2,4-DMP occurs in approximately two months (U.S. EPA, 1979); however, no environmental conditions were described.

II. EXPOSURE

A. Water

U.S. EPA (1979) reported that no specific data are available on the amounts of 2,4-DMP in drinking water. The concentrations of 2,4-DMP present in drinking water vary depending on the amounts present in untreated water

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and on the efficiency of water treatment systems in removing phenolic compounds. In the U.S., the gross annual discharge of 2,4-DMP into waters was estimated to be 100 tons in 1975 (Versar, 1975). Manufacturing was the largest source of the discharge. Leachates from municipal and industrial wastes also contain the compound (U.S. EPA, 1979).

Hoak (1957) determined that, at 30°C, the odor threshold for 2,4-DMP was 55.5 µg/l.

B. Food

DMP's occur naturally in tea (Kaiser, 1967), tobacco (Baggett and Morie, 1973; Spears, 1963), marijuana (Hoffmann, et al. 1975), and a conifer (Gornostaeva, et al. 1977). There is no evidence to suggest that dimethylphenols occur in many plants used for food; however, it may be assumed that trace amounts are ingested (U.S. EPA, 1979).

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for 2,4-DMP to be 340 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on the measured steady-state bioconcentration studies in the bluegill.

C. Inhalation

2,4-Dimethylphenol has been found in commercial degreasing agents (NIOSH, 1978), cresol vapors (Corcos, 1939), cigarette smoke condensates (Baggett and Morie, 1973; Hoffmann and Wynder, 1963; Smith and Sullivan, 1964), marijuana cigarette smoke (Hoffmann, et al. 1975) and vapors from the combustion and pyrolysis of building materials (Tsuchiya and Sumi, 1975). Concentrations in smoke condensates from six different brands of American cigarettes ranged from 12.7 to 20.8 mg/cigarette without filters and 4.4 to 9.1 mg/cigarette with filters (Hoffman and Wynder, 1963).

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There is no evidence in the available literature indicating that humans are exposed to 2,4-DMP other than as components of complex mixtures. Adverse health effects have been found in workers exposed to mixtures containing amounts of 2,4-DMP; however, the effects were not attributed to dimethylphenol exposure per se (NIOSH, 1978).

D. Dermal

Absorption through the skin is thought to be the primary route of human exposure to complex mixtures containing 2,4-DMP (U.S. EPA, 1979).

III. PHARMACOKINETICS

A. Absorption

2,4-DMP is readily absorbed through the skin (U.S. EPA, 1979). The dermal LD_{50} for molten 2,4-DMP is 1,040 mg/kg in the rat (Uzhdovini, et al. 1974).

B. Distribution

U.S. EPA (1979) found no pertinent data on the distribution of 2,4-DMP in humans or animals in the available literature. 2,6- or 3,4-DMP given orally to rats for eight months caused damage to the liver, spleen, kidneys, and heart (Maazik, 1968).

C. Metabolism

Urinary metabolites, resulting from oral administration of 850 mg of 2,4-DMP to rabbits, were primarily ether-soluble acid and ether glucuronide, with lesser amounts of ethereal sulfate, ester glucuronide and free non-acidic phenol (Bray, et al. 1950). Similar metabolism of the other dimethylphenol positional isomers was reported.

D. Excretion

A study done on rabbits by Bray, et al. (1950) indicates rapid metabolism and excretion of 2,4-DMP.

IV. EFFECTS

A. Carcinogenicity

Epidemiologic studies of workers exposed to 2,4-DMP were not located in the available literature.

In a carcinogenicity bioassay, 26 female Sutter mice were dermally exposed to 25 µl of 20 percent 2,4-DMP in benzene twice weekly for 24 weeks. Twelve percent of the exposed mice developed carcinomas; however, benzene was not evaluated by itself in this study (Boutwell and Bosch, 1959). In a related study, Boutwell and Bosch (1959) applied 25 µl of 20 percent 2,4-DMP in benzene to the skin of female Sutter mice twice a week for 23 weeks following a single application of a subcarcinogenic dose (75 µg) of DMBA. Papillomas or carcinomas developed in 18 percent of the mice, indicating that 2,4-DMP may be a promoting agent for carcinogenesis.

Fractions of cigarette smoke condensate containing phenol, methylphenols and 2,4-DMP have been shown to promote carcinogenesis in mouse skin bioassays (Lazar, et al. 1966; Bock, et al. 1971; Roe, et al. 1959).

B. Mutagenicity, Teratogenicity and Other Reproductive Effects

Pertinent data could not be located in the available literature regarding mutagenicity, teratogenicity and other reproductive effects.

C. Chronic Toxicity

Pertinent information concerning the chronic effects of 2,4- DMP was not located in the available literature(U.S. EPA, 1979); however, data was available on other positional isomers. Examination of rats treated orally with 6 mg/kg of 2,6-dimethylphenol or 14 mg/kg of 3,4-dimethylphenol for eight months revealed fatty dystrophy and atrophy of the hepatic cells,

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hyaline-droplet dystrophy in the kidneys, proliferation of mycloid and reticular cells, atrophy of the lymphoid follicles of the spleen, and parenchymatous dystrophy of the heart cells (Maazik, 1968).

D. Other Relevant Information

Tests on isolated rat lungs indicate that 2,4-DMP may inhibit vasoconstriction, most likely due to its ability to block ATP (Lunde, et al. 1968). Because of 2,4-DMP's physiological activity, U.S. EPA (1979) reports that chronic exposure to the compound may cause adverse health effects in humans.

V. AQUATIC TOXICITY

Pertinent data could not be located in the available literature regarding any saltwater species.

A. Acute Toxicity

A reported 96-hour LC_{50} value for juvenile fathead minnows is 16,750 µg/l (U.S. EPA, 1979). For the freshwater invertebrate Daphnia magna, the observed 48-hour LC_{50} is 2,120 µg/l (U.S. EPA, 1979).

B. Chronic Toxicity

Based on an embryo-larval test with the fathead minnow, Pimephales promelas, the derived chronic value is 1,100 µg/l (U.S. EPA, 1978). No chronic values are available for invertebrate species.

C. Plant Effects

Based on chlorosis effects, the reported LC_{50} for duckweed, Lemna minor, is 292,800 µg/l for 2,4-dimethylphenol exposure (Blackman, et al. 1955).

D. Residues

A bioconcentration factor of 150 was obtained for the bluegill. The biological half-life in the bluegill is less than one day, indicating

that 2,4-dimethylphenol residues are probably not a potential hazard for aquatic organisms (U.S. EPA, 1978).

VI. EXISTING GUIDELINES AND STANDARDS

Standards have not been promulgated for 2,4-DMP for any sector of the environment or workplace.

A. Human

The draft criterion for 2,4-dimethylphenol in water recommended by the U.S. EPA (1979) is 15.5 µg/l based upon the prevention of adverse effects attributable to the organoleptic properties of 2,4-DMP.

B. Aquatic

For 2,4-dimethylphenol, the draft criterion to protect freshwater aquatic life is 38 µg/l as a 24-hour average; the concentration should not exceed 86 µg/l at any time. No criterion exists for saltwater species (U.S. EPA, 1979).

2,4-DIMETHYLPHENOL

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No. 88

Dimethyl Phthalate

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

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DIMETHYL PHTHALATE

SUMMARY

Dimethyl phthalate has been shown to produce mutagenic effects in the Ames Salmonella assay.

Administration of dimethyl phthalate to pregnant rats by i.p. injection has been reported to produce teratogenic effects in a single study. Other reproductive effects produced by dimethyl phthalate included impaired implantation and parturition in rats following i.p. administration.

Chronic feeding studies in female rats have indicated an effect of dimethyl phthalate on the kidneys. There is no evidence to indicate that dimethyl phthalate has carcinogenic effects.

Among the four aquatic species examined, freshwater fish and invertebrates appeared to be more sensitive than their marine counterparts. Acute toxicity values at concentrations of 49,500 µg/l were obtained for freshwater fish. Criterion could not be drafted because of insufficient data concerning the toxic effects of dimethyl phthalates to aquatic organisms.

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DIMETHYL PHTHALATE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Phthalate Esters (U.S. EPA, 1979a).

Dimethyl phthalate (DMP) is a diester of the ortho form of benzene dicarboxylic acid. The compound has a molecular weight of 194.18, specific gravity of 1.189, boiling point of 282°C, and a solubility of 0.5 gms in 100 ml of water (U.S. EPA, 1979a).

DMP is used as a plasticizer for cellulose ester plastics and as an insect repellant.

Current Production: 4.9×10^3 tons/year in 1977 (U.S. EPA, 1979a).

Phthalates have been detected in soil, air, and water samples; in animal and human tissues; and in certain vegetation. Evidence from in vitro studies indicates that certain bacterial flora may be capable of metabolizing DMP to the monoester form (Englehardt, et al. 1975).

For additional information regarding the phthalate esters in general, the reader is referred to the EPA/ECAO Hazard Profile on Phthalate Esters (U.S. EPA, 1979b).

II. EXPOSURE

Phthalate esters appear in all areas of the environment. Environmental release of phalates may occur through leaching of the compound from plastics, volatilization from plastics, or the incineration of plastic items. Sources of human exposure to phthalates include contaminated foods and fish, dermal application, and parenteral administration

by use of plastic blood bags, tubing, and infusion devices (mainly DEHP release). Relevant factors in the migration of phthalate esters from packaging materials to food and beverages are: temperature, surface area contact, lipoidial nature of the food, and length of contact (U.S. EPA, 1979a).

Monitoring studies have indicated that most water phthalate concentrations are in the ppm range, or 1-2 µg/liter (U.S. EPA, 1979a). Industrial air monitoring studies have measured air levels of phthalates from 1.7 to 66 mg/m^3 (Milkov, et al. 1973). Information on levels of DMP in foods is not available.

The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor for DMP to be 130 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on the measured steady-state bioconcentration studies in bluegills.

III. PHARMACOKINETICS

Specific information is not available on the absorption, distribution, metabolism, or excretion of DMP. The reader is referred to a general coverage of phthalate metabolism in the phthalate ester hazard profile (U.S. EPA, 1979b).

IV. EFFECTS

A. Carcinogenicity

Pertinent data could not be located in the available literature.

B. Mutagenicity

Dimethyl phthalate has been shown to produce mutagenic effects in the Ames Salmonella assay (Rubin, et al. 1979).

C. Teratogenicity

Administration of DMP to pregnant rats by i.p. injection has been reported to produce teratogenic effects (Singh, et al. 1972). Intraperitoneal administration of DMP to pregnant rats in another study did not result in teratogenic effects (Peters and Cook, 1973).

D. D. Other Reproductive Effects

Adverse effects by DMP on implantation and parturition were reported by Peters and Cook (1973) following i.p. administration of the compound to rats.

E. Chronic Toxicity

Two-year feeding studies with dietary DMP have produced some kidney effects in female rats and minor growth effects (Draize, et al. 1948).

V. AQUATIC TOXICITY

A. Acute Toxicity

Two freshwater species were examined for acute toxicity from dimethyl phthalate exposure. The 48-hour static LC_{50} for the Cladoceran, Daphnia magna, was 33,000 µg/l (U.S. EPA, 1978). The 96-hour static LC_{50} value for the bluegill, Lepomis macrochirus, was 49,500 µg/l. For marine species, 96-hour static LC_{50} values for the sheepshead minnow, Cyprinodon variegatus, and mysid shrimp, Mysidopsis bahia, were 58,000 and 73,700 µg/l, respectively.

B. Chronic Toxicity

Pertinent information could not be located in the available literature.

C. Plant Effects

Effective concentrations based on chlorophyl a content and cell number for the freshwater algae Selenastrum capricornutum and the marine algae Skeletonema costatum ranged from 39,800 to 42,700 µg/l and 26,100 to 29,800 µg/l, respectively.

D. Residues

A bioconcentration factor of 57 was obtained for the freshwater bluegill, Lepomis macrochirus.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

Based on "no effect" levels observed in chronic feeding studies in rats and dogs, the U.S. EPA (1979a) has calculated an acceptable daily intake (ADI) level of 700 mg/day for DMP.

The recommended water quality criteria level for protection of human health is 160 mg/liter for DMP (U.S. EPA, 1979a).

B. Aquatic

The data base for toxicity of dimethyl phthalate was insufficient for drafting criterion for either freshwater or marine organisms (U.S. EPA, 1979a).

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No. 89

Dinitrobenzenes

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DINITROBENZENES

Summary

Due to the lack of available information, no assessment of the potential of dinitrobenzenes to produce carcinogenic effects, mutagenic effects, teratogenic effects, or adverse reproductive effects can be made.

Dinitrobenzene is the most potent methemoglobin-forming agent of the nitroaromatics and rapidly produces cyanosis in exposed populations.

Fish have been acutely affected by exposure to non-specified isomers of dinitrobenzene at concentrations ranging from 2,000 to 12,000 ug/l.

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DINITROBENZENE

I. INTRODUCTION

This profile is based on the Investigation of Selected Potential Environmental Contaminants: Nitroaromatics (U.S. EPA, 1976).

The dinitrobenzenes exist as the ortho, meta, or para isomers, depending on the position of the nitro group substitutents. Ortho-dinitrobenzene (1,2-dinitrobenzene, M.W. 168.1) is a white, crystalline solid with a boiling point of 319°C, a melting point of 118°C, and a specific gravity of 1.57. Meta-dinitrobenzene (1,3-dinitrobenzene) is a yellow, crystalline solid that melts at 89-90°C, boils at 300-303°C, and has a density of 1.55. Para-dinitrobenzene (1,4-dinitrobenzene) is a white, crystalline solid with a boiling point of 299°C, a melting point of 173-174°C, and a density of 1.63 (Windholz, 1976). The dinitrobenzenes have low aqueous solubility and are soluble in alcohol.

The dinitrobenzenes are used in organic synthesis, the production of dyes, and as a camphor substitute in celluloid production.

The domestic production volume of meta-dinitrobenzene in 1972 was approximately 6×10^3 tons (U.S. EPA, 1976).

Dinitrobenzenes are generally stable in neutral aqueous solutions; as the medium becomes more alkaline they may undergo hydrolysis (Murto, 1966). Para-dinitrobenzene will undergo photochemical reduction in isopropanol under nitrogen, but this reaction is quenched when the solvent is aerated (Hashimoto and Kano, 1972).

Biodegradation of dinitrobenzenes has been reported for acclimated microorganisms (Chambers, et al. 1963; Bringmann and Kuehn, 1959).

Based on the octanol/water partition coefficient, Neely et al. (1974) have estimated a low bioconcentration potential for the dinitrobenzenes.

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II. EXPOSURE

Industrial dinitrobenzene poisoning reports have shown that workers will develop intense cyanosis with only slight exposure (U.S. EPA, 1976). Exposure to sunlight or ingestion of alcohol may exacerbate the toxic effects of dinitrobenzene exposure (U.S. EPA, 1976).

Monitoring data on levels of dinitrobenzenes in water, air, or food were not found in the available literature; human exposure from these sources cannot be evaluated.

III. PHARMACOKINETICS

A. Absorption

Methemoglobin formation in workers exposed to dinitrobenzene indicates that absorption of the compound by inhalation/dermal routes occurs. Animal studies demonstrate that dinitrobenzene is absorbed following oral administration.

B. Distribution

Pertinent information on distribution of dinitrobenzenes was not found in the available literature.

C. Metabolism

Dinitrobenzene undergoes both metabolic reduction and oxidation. Animal studies indicate that the major reduction productions following oral dinitrobenzene administration were nitroaniline and phenylene diamine (35% of the administered dose) (Parke, 1961). The major oxidative metabolites of meta-dinitrobenzene were 2,4-diaminophenol (31% of initial dose) and 2-amino-4-nitrophenol (14% of initial dose). The phenols are further conjugated as glucuronides or etheral sulfates (Parke, 1961).

D. Excretion

Oral administration of radiolabelled meta-dinitrobenzene to rabbits was followed by elimination of 65-93% of the dose within two days. Excretion was almost entirely via the urine; 1-5% of the administered label was determined in the feces (Parke, 1961).

IV. EFFECTS

A. Carcinogenicity

Information on the carcinogenicity of the dinitrobenzenes was not found in the available literature.

B. Mutagenicity

Information on the mutagenicity of the dinitrobenzenes was not found in the available literature. The possible dinitrobenzene metabolite, dinitrophenol (U.S. EPA, 1979), has been reported to induce chromatid breaks in bone marrow cells of injected mice (Misra and Manna, 1971).

C. Teratogenicity

Information on the teratogenicity of the dinitrobenzenes was not found in the available literature. The possible dinitrobenzene metabolite, dinitrophenol (U.S. EPA, 1979), has produced developmental abnormalities in the sea urchin (Hagstrom and Lonning, 1966). No effects were seen following injection or oral administration of dinitrophenol to mice (Gibson, 1973).

D. Other Reproductive Effects

Pertinent information was not found in the available literature.

E. Chronic Toxicity

Dinitrobenzene is the most potent methemoglobin-forming agent of the nitroaromatics. Poisoning symptoms in humans may be potentiated by exposure to sunlight or ingestion of alcohol (U.S. EPA. 1976).

V. AQUATIC TOXICITY

A. Acute Toxicity

McKee and Wolf (1963) have presented a brief synopsis of the toxic effects of dinitrobenzenes to aquatic life. A study by LeClerc (1960) reported lethal doses of non-specific isomers of dinitrobenzene for minnows (unspecified) at concentrations of 10,000 to 12,000 µg/l in distilled water or 8,000 to 10,000 µg/l in hard water. Meinck et al. (1956) reported lethal concentration of 2,000 µg/l for unspecified dinitrobenzenes for an unspecified fish species.

B. Chronic Toxicity

Pertinent data could not be found in the available literature regarding aquatic toxicity.

C. Plant Effects

Howard et al. (1976) report that the algae Chlorella sp. displayed inhibited photosynthetic activity upon exposure to m-dinitrobenzene at a concentration of 10^{-4} M.

VI. EXISTING GUIDELINES

The 8-hour time-weighted-average (TWA) occupational exposure limit for dinitrobenzenes is 0.15 ppm (ACGIH, 1974).

DINITROBENZENES

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No. 90

4,6-Dinitro-o-cresol

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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90-2

4,6-DINITRO-O-CRESOL

SUMMARY

There is no available evidence to indicate that 4,6-dinitro-ortho-cresol (DNOC) is carcinogenic.

This compound has produced some DNA damage in Proteus mirabilis but failed to show mutagenic effects in the Ames assay or in E. coli. Available information does not indicate that DNOC produces teratogenic or adverse reproductive effects.

Human exposure incidents have shown that DNOC produces an increase in cataract formation.

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4,6-DINITRO-O-CRESOL

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Nitrophenols (U.S. EPA, 1979a).

Dinitrocresols are compounds closely related to the dinitrophenols; they bear an additional 2-position methyl group. The physical properties of 4,6-dinitro-ortho-cresol (DNOC, M.W. 198.13) include a melting point of 85.8°C and a solubility of 100 mg/l in water at 20°C (U.S. EPA, 1979a).

Dinitro-ortho-cresol is used primarily as a blossom thinning agent on fruit trees and as a fungicide, insecticide and miticide on the fruit trees during the dormant season. There is no record of current domestic manufacture of DNOC (U.S. EPA, 1979a). For additional information regarding the nitrophenols in general, the reader is referred to the Hazard Profile on Nitrophenols (U.S. EPA, 1979b).

II. EXPOSURE

The lack of monitoring data makes it difficult to assess exposure from water, inhalation, and foods. DNOC has been detected at 18 mg/l in effluents from chemical plants (U.S. EPA, 1979a).

Exposure to DNOC appears to be primarily through occupational contact (chemical manufacture, pesticide application). Contaminated water may result in isolated poisoning incidents.

The U.S. EPA (1979a) has estimated a weighted average bioconcentration factor for DNOC to be 7.5 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficient.

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III. PHARMACOKINETICS

A. Absorption

DNOC is readily absorbed through the skin, the respiratory tract, and the gastrointestinal tract (NIOSH, 1978).

B. Distribution

DNOC has been found in several body tissues; however, the compound may be bound to serum proteins, thus producing non-specific organ distribution (U.S. EPA, 1979a).

C. Metabolism

Animal studies on the metabolism of DNOC indicate that like the nitrophenols, both conjugation of the compound and reduction of the nitro groups to amino groups occurs. The metabolism of DNOC to 4-amino-4-nitro-o-cresol is a detoxification mechanism that is effective only when toxic doses of DNOC are administered (U.S. EPA, 1979a). The metabolism of DNOC is very slow in man as compared to that observed in animal studies (King and Harvey, 1953).

D. Excretion

The experiments of Parker and coworkers (1951) in several animal species indicates that DNOC is rapidly excreted following injection; however, Harvey, et al. (1951) have shown slow excretion of DNOC in volunteers given the compound orally. As in metabolism, there is a substantial difference in excretion patterns of humans vs. experimental animals.

IV. EFFECTS

A. Carcinogenicity

Pertinent data could not located in the available literature.

B. Mutagenicity

Adler, et al. (1976) have reported that DNOC shows some evidence of producing DNA damage in Proteus mirabilis. Testing of this compound in the Ames Salmonella system (Anderson, et al., 1972) or in E. coli (Nagy, et al., 1975) failed to show any mutagenic effects.

C. Teratogenicity and Other Reproductive Effects

Pertinent data could not be located in the available literature regarding teratogenicity and other reproductive effects.

D. Chronic Toxicity

Human use of DNOC as a dieting aid has produced poisoning cases at accepted therapeutic dose levels, as well as some cases of cataract development resulting from overdoses (NIOSH, 1978).

E. Other Relevant Information

DNOC is an uncoupler of oxidative phosphorylation, an effect which accounts for its high acute toxicity in mammals.

V. AQUATIC TOXICITY

Pertinent information could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A. An eight-hour TLV exposure limit of 0.2 mg/m^3 has been recommended for DNOC by the ACGIH (1971).

A preliminary draft water criterion for DNOC has been established at 12.8 µg/l by the U.S. EPA (1979a). This draft criterion has not gone through the process of public review; therefore, there is a possibility that the criterion may be changed.

B. Aquatic

Criteria for the protection of freshwater and marine aquatic organisms were not drafted due to lack of toxicological evidence (U.S. EPA, 1979a).

VI. EXISTING GUIDELINES AND STANDARDS

A. An eight-hour TLV exposure limit of 0.2 mg/m^3 has been recommended for DNOC by the ACGIH (1971).

A preliminary draft water criterion for DNOC has been established at 12.8 µg/l by the U.S. EPA (1979a). This draft criterion has not gone through the process of public review; therefore, there is a possibility that the criterion may be changed.

B. Aquatic

Criteria for the protection of freshwater and marine aquatic organisms were not drafted due to lack of toxicological evidence (U.S. EPA, 1979a).

No. 91

2,4-Dinitrophenol

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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2,4-DINITROPHENOL

Summary

There is no evidence to indicate that 2,4-dinitrophenol possesses carcinogenic activity.

Genetic toxicity testing has shown positive effects in mouse bone marrow cells and in E. coli. In vitro cell culture assays failed to show the potential for mutagenic activity of 2,4-dinitrophenol as measured by unscheduled DNA synthesis.

Teratogenic effects have been observed in the chick embryo following administration of 2,4-dinitrophenol. Studies in mammals failed to show that the compound produced any teratogenic effects. At the levels of compound used in these mammalian studies, embryotoxic effects were observed.

Human use of 2,4-dinitrophenol as a dieting aid has produced some cases of agranulocytosis, neuritis, functional heart damage, and cataract development.

For aquatic organisms LC_{50} values ranged from 620 µg/l for the bluegill to 16,700 µg/l for the fathead minnow.

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2,4-DINITROPHENOL

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Nitrophenols (U.S. EPA, 1979a).

The dinitrophenols are a family of compounds composed of the isomers resulting from nitro-group substitution of phenol at various positions. 2,4-Dinitrophenol has a molecular weight of 184.11, a melting point of 114-115°C, a density of 1.683 g/ml and is soluble in water at 0.79 g/l (U.S. EPA, 1979a).

The dinitrophenols are used as chemical intermediates for sulfur dyes, azo dyes, photochemicals, pest control agents, wood preservatives, and explosives (U.S. EPA, 1979a). The 1968 production of 2,4-dinitrophenol was 4.3×10^2 tons/yr. (U.S. EPA, 1979a).

For additional information regarding the nitrophenols as a class, the reader is referred to the Hazard Profile on Nitrophenols (1979b).

II. EXPOSURE

The lack of monitoring data for the nitrophenols makes it difficult to assess exposure from water, innalation, and foods. Nitrophenols have been detected in effluents from chemical plants (U.S. EPA, 1979a). Dermal absorption of the dinitrophenols has been reported (U.S. EPA, 1979a).

Exposure to nitrophenols appears to be primarily through occupational contact (chemical plants, pesticide application). Contaminated water may contribute to isolated poisoning incidents. The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor for 2,4-dinitrophenol to be 2.4 for the edible

portions of fish and shellfish consumed by Americans. This estimate was based on the octanol/water partition coefficients of 2,4-dinitrophenol.

III. PHARMOCOKINETICS

A. Absorption

The dinitrophenols are readily absorbed following oral, inhalation, or dermal administration (U.S. EPA, 1979a).

B. Distribution

Dinitrophenol blood concentrations rise rapidly after absorption, with little subsequent distribution or storage at tissue sites (U.S. EPA, 1979a).

C. Metabolism

Metabolism of the nitrophenols occurs through conjugation and reduction of nitro-groups to amino-groups, or oxidation to dihydric-nitrophenols (U.S. EPA, 1979a).

D. Excretion

Experiments with several animal species indicate that urinary clearance of dinitrophenols is rapid (Harvey, 1959).

VI. EFFECTS

A. Carcinogenicity

2,4-Dinitrophenol has been found not to promote skin tumor formation in mice following DMBA initiation (Bautwell and Bosch, 1959).

B. Mutagenicity

Testing of 2,4-dinitrophenol has indicated mutagenic effects in E. coli (Demerec, et al. 1951). In vitro assays of unscheduled DNA synthesis (Friedman and Staub, 1976) and DNA

damage induced during cell culture (Swenberg, et al. 1976) failed to show the potential for mutagenic activity of this compound.

C. Teratogenicity

2,4-Dinitrophenol has been shown to produce developmental abnormalities in the chick embryo (Bowman, 1967; Miyatmoto, et al. 1975). No teratogenic effects were seen following intragastric administration to rats (Wulff, et al. 1935) or intraperitoneal administration to mice (Gibson, 1973).

D. Other Reproductive Effects

Feeding of 2,4-dinitrophenol to pregnant rats produced an increase mortality in offspring (Wulff, et al., 1935); similarly, intraperitoneal administration of the compound to mice induced embryotoxicity (Gibson, 1973). The influence of this compound on maternal health may have contributed to these effects.

E. Chronic Toxicity

Use of 2,4-dinitrophenol as a human dieting aid has produced some cases of agranulocytosis, neuritis, functional heart damage, and a large number of patients suffering from cataracts (Horner, 1942).

F. Other Relevant Information

2,4-Dinitrophenol is a classical uncoupler of oxidative phosphorylation, an effect which accounts for its high acute toxicity in mammals.

A synergistic action in producing teratogenic effects in the developing chick embryo has been reported with a combination of 2,4-dinitrophenol and insulin (Landauer and Clark, 1964).

V. AQUATIC TOXICITY

A. Acute

The bluegill (*Lepomis macrochirus*) was the most sensitive aquatic organism tested, with an LC_{50} of 620 µg/l in a static, 96-hour assay (U.S. EPA, 1978). Juvenile fathead minnows (*Pimephales promelas*) were more resistant in flow through tests, with an LC_{50} of 16,720 µg/l (Phipps, et al. manuscript). The freshwater cladoceran (*Daphnia magna*) displayed a range of observed LC_{50} values of 4,090 to 4,710 µg/l (U.S. EPA, 1979a). Acute values for the marine sheepshead minnow (*Cyprinodon variegatus*) are LC_{50} values ranging from 5,500 to 29,400 µg/l (Rosenthal and Stelzer, 1970). The marine mysid shrimp (*Mysidopsis bahia*) had an LC_{50} of 4,850 µg/l (U.S. EPA, 1978).

B. Chronic Toxicity

Pertinent data could not be located in the available literature.

C. Plant Effects

Effective concentrations for freshwater plants ranged from 1,472 µg/l for duckweed (*Lemna minor*) to 50,000 µg/l for the alga (*Chlorella pyrenoidosa*) (U.S. EPA, 1979a). The marine alga (*Skeletonema costatum*) was more resistant with a reported 96-hour EC_{50} value based on cell numbers of 98,700 µg/l.

D. Residues

Based on the octanol/water partition coefficient, a bioconcentration factor of 8.1 has been estimated for 2,4-dinitrophenol for aquatic organisms with a lipid content of 8 percent.

V. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor aquatic criteria derived by U.S. EPA (1979a) which are summarized below have undergone the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

The draft water criterion for dinitrophenols, based on data describing adverse effects, has been estimated by the U.S. EPA (1979a) as 68.6 µg/l.

B. Aquatic

For protecting freshwater aquatic life, the draft criterion is 79 µg/l as a 24-hour average concentration not to exceed 180 µg/l. The marine criterion has been proposed as 37 µg/l as a 24-hour average not to exceed 84 µg/l at any time (U.S. EPA, 1979a).

To protect saltwater life, the draft criterion is 37 µg/l as a 24-hour average not to exceed 84 µg/l at any time (U.S. EPA, 1979a).

2,4-DINITROPHENOL

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No. 92

Dinitrotoluene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
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DINITROTOLUENE

SUMMARY

Most of the information on the effects of dinitrotoluene deals with 2,4-dinitrotoluene. 2,4-Dinitrotoluene induces liver cancer and mammary tumors in mice and is mutagenic in some assay systems. Information on teratogenicity was not located in the available literature. Chronic exposure to 2,4-dinitrotoluene induces liver damage, jaundice, methemoglobinemia and anemia in humans and animals.

Acute studies in freshwater fish and invertebrates suggest that 2,3-dinitrotoluene is much more toxic than 2,4-dinitrotoluene.

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DINITROTOLUENE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Dinitrotoluene (U.S. EPA, 1979).

There are six isomers of dinitrotoluene ($CH_3C_6H_3(NO_2)_2$; molecular weight 182.14), with the 2,4-isomer being the most important commercially. 2,4-Dinitrotoluene has a melting point of 71°C, a boiling point of 300°C with decomposition, and a solubility in water of 270 mg/l at 22°C. It is readily soluble in ether, ethanol, and carbon disulfide (U.S. EPA, 1979). 2,6-Dinitrotoluene has a melting point of 66°C and is soluble in alcohol. Production in 1975 was 273×10^3 tons per year for the 2,4- and 2,6- isomers combined (U.S. EPA, 1979).

Dinitrotoluene is an ingredient of explosives for commercial and military use, a chemical stabilizer in the manufacture of smokeless powder, an intermediate in the manufacture of toluene diisocyanates used in the production of urethane polymers, and a raw material for the manufacture of dyestuffs. Dinitrotoluenes are relatively stable at ambient temperatures (U.S. EPA, 1979).

II. EXPOSURE

A. Water

Data on concentration levels for dinitrotoluene were not available. Dinitrotoluene waste products are dumped into surface water or sewage by industries that manufacture dyes, isocyanates, polyurethanes and munitions (U.S. EPA, 1979).

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B. Food

According to the U.S. EPA (1979), the likelihood of dinitrotoluene existing in food is minimal since it is not used as a pesticide or herbicide.

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for 2,4-dinitrotoluene to be 5.5 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficient.

C. Inhalation

Exposure to dinitrotoluene by inhalation is most likely to occur occupationally (U.S. EPA, 1979). However, pertinent data could not be located in the available literature on atmospheric concentrations of dinitrotoluene and, thus, possible human exposure cannot be estimated.

III. PHARMACOKINETICS

A. Absorption

The absorption of ^{14}C-labeled isomers of dinitrotoluene after oral administration to rats was essentially complete within 24 hours, with 60 to 90 percent of the dose being absorbed. The 2,4- and 3,4-isomers were absorbed to a greater extent than the 3,5- and 2,5- isomers, which in turn were absorbed to a greater extent than the 2,3- and 2,6-isomers (Hodgson, et al. 1977). 2,4-Dinitrotoluene is known to be absorbed through the respiratory tract and skin (U.S. EPA, 1979).

B. Distribution

Tissue/plasma ratios of radioactivity after administration of ^{14}C-labeled dinitrotoluene to rats indicated retention of ^{14}C DNT in both the liver and kidneys but not in other tissues (Hodgson, et al., 1977). A similar experiment with tritium-labeled 2,4-dinitrotoluene (^{3}H-2,4-DNT) in the rat showed relatively high amounts of radioactivity remaining in adipose tissue, skin, and liver seven days after administration (Mori, et al., 1977).

C. Metabolism

No studies characterizing the metabolism of dinitrotoluene in mammals are available. However, on the basis of a comparison of the metabolism of 2,4-dinitrotoluene and 2,4,6-trinitrotoluene in microbial systems, and the known metabolism of 2,4,6-trinitrotoluene in mammals, the U.S. EPA (1979) speculated that the metabolites of 2,4-dinitrotoluene in mammals would be either toxic and/or carcinogenic.

D. Excretion

In studies involving oral administration of ^{14}C-dinitrotoluene or ^{3}H-2,4-dinitrotoluene to rats (Hodgson, et al., 1977; Mori, et al., 1977), elimination of radioactivity occurred mainly in urine and feces. No radioactivity was recovered in the expired air. About 46 percent of the administered dose in the latter study was excreted in the feces and urine during the seven days following administration.

IV. EFFECTS

A. Carcinogenicity

2,4-Dinitrotoluene fed to rats and mice for two years produced dose-related increases in fibromas of the skin in male rats and fibroadenomas of the mammary gland in female rats. All of these were benign tumors. No statistically significant increase in tumor incidence was noted in mice (Natl. Cancer Inst., 1978).

In a second bioassay of rats and mice fed 2,4-dinitrotoluene for two years, the findings in rats included a significant increase of hepatocellular carcinomas and neoplastic nodules in the livers of females, a significant increase of mammary gland tumors in females, and a suspicious increase of hepatocellular carcinomas of the liver in males. Male mice had a highly significant increase of kidney tumors (Lee, et al., 1978).

B. Mutagenicity

2,4-Dinitrotoluene was mutagenic in the dominant lethal assay and in Salmonella typhimurium strain TA1535 (Hodgson, et al. 1976). Cultures of lymphocytes and kidney cells derived from rats fed 2,4-dinitrotoluene had significant increases in the frequency of chromatid gaps but not in translocations or chromatid breaks (Hodgson, et al., 1976).

The mutagenic effects of products from ozonation or chlorination of 2,4-dinitrotoluene and other dinitrotoluenes

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were negative in one study (Simmon, et al., 1977), and, for products of ozonation alone, were ambiguous in another study (Cotruvo, et al., 1977).

C. Teratogenicity and other Reproductive Effects

Pertinent data could not be located in the available literature.

D. Chronic Toxicity

Chronic exposure to 2,4-dinitrotoluene may produce liver damage, jaundice, methemoglobinemia and reversible anemia with reticulocytosis in humans and animals (Linch, 1974; Key, et al. 1977; Proctor and Hughes, 1978; Kovalenko, 1973).

E. Other Relevant Information

Animals were more resistant to the toxic effects of 2,4-dinitrotoluene administered in the diet when given diets high in fat or protein (Clayton and Baumann, 1944, 1948; Shils and Goldwater, 1953) or protein (Shils and Goldwater, 1953).

Alcohol has a synergistic effect on the toxicity of 2,4-dinitrotoluene (Friedlander, 1900; McGee, et al., 1942).

In subacute studies (13 weeks), 2,4- and 2,6-dinitrotoluene caused methemoglobinemia, anemia with reticulocytosis, gliosis and demyelination in the brain, and atrophy with aspermatogenesis of the testes in several species (Ellis, et al., 1976).

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V. AQUATIC TOXICITY

A. Acute Toxicity

Static assays with the freshwater bluegill (Lepomis macrochirus) produced a 96-hour LC_{50} value of 330 µg/l for 2,3-dinitrotoluene (U.S. EPA, 1978), while the same assay with the fathead minnow (Pimephales promelas) produced a 96-hour LC_{50} value of 31,000 µg/l for 2,4-dinitrotoluene (U.S. Army, 1976). The greater toxicity of 2,3-dinitrotoluene when compared to that of 2,4-dinitrotoluene, was demonstrated in 48-hour static assays with the freshwater cladoceran, Daphnia magna, with LC_{50} values of 660 µg/l(U.S. EPA, 1978) and 35,000 µg/l (U.S. Army, 1976) being reported. A single marine fish, sheepshead minnow (Cyprinodon variegatus), has been tested for adverse acute effects of 2,3-dinitrotoluene. A 96-hour static assay LC_{50} value of 2,280 µg/l was reported (U.S. EPA, 1978). For marine invertebrates a 96-hour static LC_{50} value of 590 µg/l was obtained for the mysid shrimp (Mysidopsis bahia) with 2,3-dinitrotoluene.

B. Chronic Toxicity

The sole chronic study examining the effects of 2,3-dinitrotoluene in an embryo-larval assay on the fathead minnow produced a chronic value of 116 µg/l based on reduced survival of these stages. No marine chronic data were presented (U.S. EPA, 1979).

C. Plant Effects

Concentrations of 2,3-dinitrotoluene that caused 50 percent adverse effects in cell numbers or chlorophyll

a in the freshwater algae, Selenastrum capricornutum, were 1,370 or 1,620 µg/l, respectively. These same effects measured in the marine algae, Skeletonema costatum, showed it to be more sensitive. EC_{50} values were 370 or 400 µg/l, respectively.

D. Residues

A bioconcentration factor of 19 was obtained for aquatic organisms having a lipid content of 8 percent (U.S. EPA, 1979).

VI. EXISTING STANDARDS AND GUIDELINES

Neither the human health nor aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria may be changed.

A. Human

Based on the induction of fibroadenomas of the mammary gland in female rats (Lee, et al., 1978), and using the "one-hit" model, the U.S. EPA (1979) has estimated levels of 2,4-dinitrotoluene in ambient water which will result in specified risk levels of human cancer:

Exposure Assumptions (per day)	Risk Levels and Corresponding Draft Criteria			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish.		7.4 ng/l	74.0 mg/l	740 ng/l
Consumption of fish and shellfish only.		.156 µg/l	1.56 µg/l	15.6 µg/l

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The American Conference of Governmental Industrial Hygienists (1978) recommends a TLV-time weighted average for 2,4-dinitrotoluene of 1.5 mg/m^3 with a short term exposure limit of 5 mg/m^3.

B. Aquatic

A criterion to protect freshwater life has been drafted as 620 µg/l for a 24-hour average not to exceed 1,400 µg/l for 2.4-dinitrotoluene and 12 µg/l not to exceed 27 µg/l for 2,3-dinitrotoluene. For marine environments a criterion has been drafted for 2,3-dinitrotoluene as a 4.4 µg/l as a 24-hour average not to exceed 10 µg/l. Data was insufficient to draft a criterion for 2,4-dinitrotoluene for marine environments.

DINITROTOLUENE

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No. 93

2,4-Dinitrotoluene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated 2,4-dinitrotoluene and has found sufficient evidence to indicate that this compound is carcinogenic.

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2,4-DINITROTOLUENE

Summary

2,4-Dinitrotoluene induces liver cancer and mammary tumors in mice and is mutagenic in some assay systems. Information on teratogenicity was not located in the available literature. Chronic exposure to 2,4-dinitrotoluene induces liver damage, jaundice, methemoglobinemia and anemia in humans and animals.

Two acute studies, one on freshwater fish and the other on freshwater invertebrates, provide the only data of 2,4-dinitrotoluene's adverse effects on aquatic organisms. Acute LC_{50} values were reported as 17,000 and 30,000 µg/l. No marine data are available.

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2,4-DINITROTOLUENE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Dinitrotoluene (U.S. EPA, 1979a).

2,4-Dinitrotoluene (2,4-DNT) has a melting point of 71°C, a boiling point of 300°C with decomposition, and a solubility in water of 270 mg/l at 22°C. It is readily soluble in ether, ethanol, and carbon disulfide (U.S. EPA, 1979a).

Production in 1975 was 273 x 10^3 tons/year for the 2,4- and 2,6-isomers combined (U.S. EPA, 1979a). 2,4-Dinitrotoluene is an ingredient in explosives for commercial and military use, a chemical stabilizer in the manufacture of smokeless powder, an intermediate in the manufacture of toluene diisocyanates used in the production of urethane polymers, and a raw material for the manufacture of dye-stuffs. Dinitrotoluenes are relatively stable at ambient temperatures (U.S. EPA, 1979a). For additional information regarding the dinitrotoluenes in general, the reader is referred to the EPA/ECAO Hazard Profile on Dinitrotoluenes (U.S. EPA, 1979b).

II. EXPOSURE

A. Water

Data on concentration levels of 2,4-DNT in water were not available. Dinitrotoluene waste products are dumped into surface water or sewage by industries that manufacture dyes, isocyanates, polyurethanes and munitions (U.S. EPA, 1979a).

B. Food

According to the U.S. EPA (1979a), the likelihood of 2,4-dinitrotoluene existing in food is minimal since it is not used as a pesticide or herbicide.

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The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor for 2,4-dinitrotoluene to be 5.5 for edible portions of fish and shellfish consumed by Americans. This estimate was based on the octanol/water partition coefficient.

C. Inhalation

Exposure to dinitrotoluene by inhalation is most likely to occur occupationally (U.S. EPA, 1979a). However, pertinent data could not be located in the available literature on atmospheric concentrations of dinitrotoluene; thus, possible human exposure cannot be estimated.

III. PHARMACOKINETICS

A. Absorption

The absorption of ^{14}C-labeled isomers of dinitrotoluene after oral administration to rats was essentially complete within 24 hours, with 60 to 90 percent of the dose being absorbed. The 2,4-and 3,4-isomers were absorbed to a greater extent than the 3,5- and 2,5-isomers, which in turn were absorbed to a greater extent than the 2,3- and 2,6-isomers (Hodgson, et al. 1977). From toxicity studies, 2,4-Dinitrotoluene is known to be absorbed through the respiratory tract and skin (U.S. EPA, 1979a).

B. Distribution

Tissue/plasma ratios of radioactivity after administration of ^{14}C-labeled dinitrotoluene (DNT) to rats indicated retention of ^{14}C 2,4-DNT in both liver and kidneys but not in other tissues (Hodgson, et al. 1977). A similar experiment with tritium-labeled 2,4-dinitrotoluene (^{3}H-2,4-DNT) in the rat showed relatively high amounts of radioactivity remaining in adipose tissue, skin, and liver seven days after administration (Mori, et al. 1977).

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C. Metabolism

No studies characterizing the metabolism of 2,4-dinitrotoluene in mammals are available. However, on the basis of a comparison of the metabolism of 2,4-dinitrotoluene and 2,4,6-trinitrotoluene in microbial systems, and the metabolism of 2,4,6-trinitrotoluene in mammals, the U.S. EPA (1979a) speculated that the metabolites of 2,4-dinitrotoluene in mammals would be either toxic and/or carcinogenic.

D. Excretion

In studies involving oral administration of ^{14}C-dinitrotoluene or ^{3}H-2,4-dinitrotoluene to rats (Hodgson, et al. 1977; Mori, et al, 1977), elimination of radioactivity occurred mainly in urine and feces. No radioactivity was recovered in the expired air. About 46 percent of the administered dose in the latter study was excreted in the feces and urine during the seven days following administration.

IV. EFFECTS

A. Carcinogenicity

2,4-Dinitrotoluene fed to rats and mice for two years produced dose-related increases in fibromas of the skin in male rats and fibroadenomas of the mammary gland in female rats. These tumors were benign. No statistically significant reponse was noted in mice (Natl. Cancer Inst., 1978).

In a second bioassay of rats and mice fed 2,4-dinitrotoluene for two years, the findings in rats included a significant increase of hepatocellular carcinomas and neoplastic nodules in the livers of females, a significant increase of mammary gland tumors in females, and a suspicious increase of hepatocellular carcinomas of the liver in males. Mice had a highly significant increase of kidney tumors in males (Lee, et al. 1978).

B. Mutagenicity

2,4-Dinitrotoluene was mutagenic in the dominant lethal assay and in Salmonella typhimurium strain TA 1535 (Hodgson, et al. 1976). Cultures of lymphocytes and kidney cells derived from rats fed 2,4-dinitrotoluene had significant increases in the frequency of chromatid gaps but not in translocations or chromatid breaks (Hodgson, et al. 1976).

The mutagenic effects of products from ozonation or chlorination of 2,4-dinitrotoluene and other dinitrotoluenes were negative in one study (Simmon, et al. 1977) and, of products from ozonation alone, were ambiguous in another study (Cotruvo, et al. 1977).

C. Teratogenicity and Other Reproductive Effects

Pertinent data could not be located in the available literature.

D. Chronic Toxicity

Chronic exposure to 2,4-dinitrotoluene may produce liver damage, jaundice, methemoglobinemia and reversible anemia with reticulocytosis in humans and animals (Linch, 1974; Key, et al. 1977; Proctor and Hughes, 1978; Kovalenko, 1973).

E. Other Relevant Information

Animals were more resistant to the toxic effects of 2,4-dinitrotoluene administered in the diet when given diets high in fat (Clayton and Baumann, 1944, 1948; Shils and Goldwater, 1953) or protein (Shils and Goldwater, 1953).

Alcohol has a synergistic effect on the toxicity of 2,4-dinitrotoluene (Friedlander, 1900; McGee, et al. 1942).

In subacute studies (13 weeks) of several species, 1,2,4-dinitrotoluene caused methemoglobinemia, anemia with reliculocytasis, gliosis, and demyelination in the brain, and atrophy with aspermatogenesis of the testes (Ellis et al., 1976).

V. AQUATIC TOXICITY

A. Acute Toxicity

The only toxicity data available for the effects of 2,4-dinitrotoluene in aquatic animals are from a single freshwater fish and invertebrate species (U.S. Army, 1976). A 96-hour static LC_{50} value for the fathead minnow (Pimephales promelas) was reported as 31,000 µg/l and a 48-hour static LC_{50} value for the cladoceran, Daphnia magna, was reported as 35,000 µg/l.

B. Chronic Toxicity and Plant Effects

Pertinent data could not be located in the available literature.

C. Residues

A bioconcentration factor of 19 was obtained for 2,4-dinitrotoluene.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria may be changed.

A. Human

Based on the induction of fibroadenomas of the mammary gland in female rats (Lee, et al. 1978), and using the "one-hit" model, the U.S. EPA (1979a) has estimated levels of 2,4-dinitrotoluene in ambient water which will result in specified risk levels of human cancer:

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Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria			
	0	10^{-7}	10^{-6}	10^{-5}
Consumption of 2 liters of drinking water and 18.7 grams fish and shellfish.		7.4 ng/l	74.0 ng/l	740 ng/l
Consumption of fish and shellfish only.		.156 µg/l	1.56 µg/l	15.6 µg/l

The American Conference of Governmental Industrial Hygienists (1978) recommends a TLV-time-weighted average for 2,4-dinitrotoluene of 1.5 mg/m^3 with a short term exposure limit of 5 mg/m^3.

B. Aquatic

A criterion has been drafted for protecting freshwater life from the toxic effects of 2,4-dinitrotoluene. A 24-hour average concentration of 620 µg/l, not to exceed 1,400 µg/l, has been proposed. Data are insufficient for drafting a marine criterion.

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No. 94

2,6-Dinitrotoluene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

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2,6-Dinitrotoluene

SUMMARY

2,6-Dinitrotoluene is known to cause methemoglobinemia in cats, dogs, rats, and mice. When administered orally to these animals for a maximum of thirteen weeks, the major effects seen in addition to the blood effects were depressed spermatogenesis, degeneration of the liver, bile duct hyperplasia, incoordination and rigid paralysis of the hind legs, and kidney degeneration.

Positive results were obtained with mutagenicity testing in a number of Salmonella typhimurium strains.

2,6-DNT has been found in tap water in the United States. The nitro groups on the aromatic ring retard degeneration so there is a potential for it to accumulate in the aquatic environment.

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Dinitrotoluene (U.S. EPA, 1979b) and a U.S. EPA report entitled "Investigation of Selected Potential Environmental Contaminants: Nitroaromatics" (1976).

2,6-Dinitrotoluene (2,6-DNT; $C_7H_6N_2O_4$; molecular weight 182.14) is a solid at room temperature. It is in the shape of rhombic needles and is soluble in ethanol. Its melting point is 66°C and its density is 1.28 at 111°C (Weast, 1975).

A review of the production range (includes importation) statistics for 2,6-dinitrotoluene (CAS. No. 606-20-2) which is

listed in the initial TSCA Inventory (1979a) has shown that between 50,000,000 and 100,000,000 pounds of this chemical were produced/imported in 1977.*/

Mixtures of the dinitrotoluene isomers are intermediates in the manufacture of toluene diisocyanates, toluene diamines and trinitrotoluene (Wiseman, 1972). Dinitrotoluene (both 2,4- and 2,6-) is an ingredient in explosives for commercial and military use and is also used as a chemical stabilizer in the manufacture of smokeless powder (U.S. EPA, 1979b).

II. EXPOSURE

A. Environmental Fate

Based on the photodecomposition of trinitrotoluene (TNT) described by Burlinson et al. (1973), 2,6-dinitrotoluene would be expected to react photochemically. Decomposition of 65% of the TNT had occurred when the decomposition products were examined.

2,6-Dinitrotoluene would be expected to biodegrade to a limited extent. The nitro groups retard biodegradation and studies with soil microflora have shown that mono- and di-substituted nitrobenzenes persist for more than 64 days (Alexander and Lustigmann, 1966). McCormick et al. (1976) and Bringmann and Kuehn (1971) reported microbial degradation of 2,6-DNT by anaerobic and aerobic bacteria, respectively.

*/ This production range information does not include any production/importation data claimed as confidential by the person(s) reporting for the TSCA inventory, nor does it include any information which would compromise Confidential Business Information. The data submitted for the TSCA Inventory, including production range information, are subject to the limitations contained in the Inventory Reporting

B. Bioconcentration

In general nitroaromatic compounds do not have high bioconcentration potential based on calculations using their octanol-water partition coefficients. They are not expected to biomagnify based on their water solubility (U.S. EPA, 1976).

C. Environmental Occurrence

2,6-Dinitrotoluene has been identified in tap water in the United States (Kopfler and Melton, 1975). Its environmental contamination would come almost exclusively from the chemical plants where it is produced. It was detected in the water effluent from a TNT plant in Radford, Virginia at concentrations of 3.39 to 56.3 ppm. It was also found in the raw waste of a DNT plant at 150 ppm. The raw effluent contained 0.68 ppm and the pond effluent 0.02 ppm (U.S. EPA, 1976).

III. PHARMACOKINETICS

2,6-Dinitrotoluene can enter the body through inhalation of vapors or dust particles, ingestion of contaminated food, and absorption through the skin (EPA, 1979b). Hodgson et al. (1977) traced the pathway of ^{14}C labeled di- and tri-substituted nitrotoluenes after oral administration of the compounds to rats. All of the compounds were well absorbed with 60 to 90% absorption after 24 hours. The radiolabel was found in the liver, kidneys and blood but not in other organs; none was found in the expired air indicating that the aromatic ring was not broken down through metabolism of the compounds. Most of the labeled compounds were

Regulations (40 CFR 710).

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eliminated in the urine as metabolites; biliary excretion was also an important elimination pathway.

IV. HEALTH EFFECTS

A. Carcinogenicity

No carcinogenicity testing of 2,6-DNT has been reported in the literature. The National Cancer Institute conducted a bioassay to determine the carcinogenicity of 2,4-DNT by administering it to rats and mice in their diet. 2,4-DNT induced benign tumors in male and female rats, however, the benign tumors were not considered a sufficient basis for establishing carcinogenicity. The assay produced no evidence of carcinogenicity of the compound in mice (NCI, 1978).

B. Mutagenicity

Simmon et al. (1977) tested 2,6-dinitrotoluene for mutagenicity in Salmonella typhimurium. Positive results were obtained with strains TA1537, TA1538, TA98, and TA100, but not TA1535. These results were obtained without metabolic activation.

C. Other Toxicity

1. Chronic

The subchronic toxicity of 2,6-dinitrotoluene was determined by oral administration to dogs, rats, and mice for about 13 weeks. The primary effects were on red blood cells, the nervous system, and the testes. Both dogs and rats had decreased muscular coordination primarily in the hind legs, rigidity in extension of the hind legs, decreased appetite, and weight loss. The

mice experienced only the decreased appetite and weight loss. All of the animals had methemoglobinemia, and anemia with reticulocytosis. The tissue lesions seen were extramedullary hematopoeisis in the spleen and liver, gliosis and demyelination in the brain, and atrophy with aspermatogenesis in the testes (Ellis et al., 1976). Methemoglobinemia was also found in cats administered 2,6-DNT (U.S. EPA, 1979b).

2. Acute

Oral LD50's have been reported for rats and mice. They are 180 mg/kg and 1,000 mg/kg respectively (Vernot et al., 1977). A mixture of 2,4-DNT and 2,6-DNT was applied to the skin of rabbits in a series of 10 doses over a two week period and no cumulative toxicity was found (U.S. EPA, 1976).

VI. EXISTING GUIDELINES

The OSHA standard for 2,6-DNT in air is a time-weighted average of 1.5 mg/m^3 (39 FR 23540).

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No. 95

Di-n-octyl Phthalate

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DI-n-OCTYL PHTHALATE

Summary

Di-n-octyl phthalate has produced teratogenic effects following i.p. injection of pregnant rats. This same study has also indicated some increased resorptions and fetal toxicity.

Evidence is not available indicating mutagenic or carcinogenic effects of di-n-octyl phthalate.

Data pertaining to the aquatic toxicity of di-n-octyl phthalate is not available.

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DI-n-OCTYL PHTHALATE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Phthalate Esters (U.S. EPA, 1979a).

Di-n-octyl phthalate (DOP) is a diester of the ortho form of benzene dicarboxylic acid. The compound has a molecular weight of 391.0, specific gravity of 0.978, boiling point of 220°C at 5 mm Hg, and is insoluble in water.

DOP is used as a plasticizer in the production of certain plastics.

Current Production: 5.8×10^3 tons/year in 1977 (U.S. EPA, 1979a).

Phthalates have been detected in soil, air, and water samples; in animal and human tissues, and in certain vegetation. Evidence from *in vitro* studies indicates that certain bacterial flora may be capable of metabolizing DOP to the monoester form (Engelhardt, et al. 1975). For additional information regarding the phthalate esters in general, the reader is referred to the EPA/ECAO Hazard Profile on Phthalate Esters (U.S. EPA 1979b).

II. EXPOSURE

Phthalate esters appear in all areas of the environment. Environmental release of phthalates may occur through leaching of the compound from plastics, volatilization from plastics, or the incineration of plastic items. Sources of human exposure to phthalates include contaminated foods and fish, dermal application, and parenteral administration by use of plastic blood bags, tubings, and infusion devices (mainly DEHP release). Relevant factors in the migration of phthalate esters from packaging materials to food and beverages are: temperature, surface area contact, lipoidal nature of the food, and length of contact (U.S. EPA, 1979a).

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Monitoring studies have indicated that most water phthalate concentrations are in the ppm range, or 1-2 µg/liter (U.S. EPA, 1979a). Industrial air monitoring studies have measured air levels of phthalates from 1.7 to 66 mg/m^3 (Milkov, et al. 1973).

Information on levels of DOP in foods is not available. Bio-concentration factor is not available for DOP.

III. PHARMACOKINETICS

Specific information could not be located on the absorption, distribution, metabolism, or excretion of DOP. The reader is referred to a general coverage of phthalate metabolism (U.S. EPA, 1979b).

IV. EFFECTS

A. Carcinogenicity

Pertinent data could not be located in the available literature.

B. Mutagenicity

Pertinent data could not be located in the available literature.

C. Teratogenicity

Administration of DOP to pregnant rats by i.p. injection has been reported to produce some teratogenic effects, although less so than several other phthalates tested (Singh, et al. 1972).

D. Other Reproductive Effects

An increased incidence of resorption and fetal toxicity was produced following i.p. injection of pregnant rats with DOP (Singh, et al. 1972).

E. Chronic Toxicity

Pertinent data could not be located in the available literature.

V. AQUATIC TOXICITY

Pertinent data could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

Pertinent data concerning the acceptable daily intake (ADI) level in humans of DOP could not be located in the available literature.

Recommended water quality criterion level for protection of human health is not available for DOP.

B. Aquatic

Pertinent data is not available pertaining to the aquatic toxicity of di-n-octyl phthalate; therefore, no criterion could be drafted.

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DI-N-OCTYL PHTHALATE

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No. 96

1,2-Diphanylhydrazine

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated 1,2-diphenylhydrazine and has found sufficient evidence to indicate that this compound is carcinogenic.

1,2-DIPHENYLHYDRAZINE

Summary

The adverse effects of exposure to 1,2-diphenylhydrazine include damage to both the kidney and liver. Acute LD_{50} values have ranged from 300 to 960 mg/kg in experimentally dosed rats. No data concerning the absorption, distribution, or excretion of the 1,2-diphenylhydrazine have been generated. Benzidine has been identified as a metabolite in urine of rats exposed to the chemical. Diphenylhydrazine is carcinogenic in both sexes of rats and in female mice.

The only aquatic toxicity data for diphenylhydrazine are for freshwater organisms. Acute toxicity levels of 270 and 4,100 µg/l were reported for bluegill and Daphnia magna, respectively, and a single chronic value of 251 µg/l was reported for Daphnia magna.

1,2-DIPHENYLHYDRAZINE

I. INTRODUCTION

This profile is based primarily on the Ambient Water Quality Criteria Document for Diphenylhydrazine.

Diphenylhydrazine (DPH) has a molecular weight of 184.24, a melting point of 131°C and a boiling point of 220°C. DPH is slightly soluble in water and is very soluble in benzene, ether and alcohol.

The symmetrical isomer of diphenylhydrazine, 1,2-diphenylhydrazine is used in the synthesis of benzidine for use in dyes, and in the synthesis of phenylbutazone, an anti-arthritic drug.

The reported commercial production of more than 1000 pounds annually, as of 1977, is most likely an underestimation of the total amount of diphenylhydrazine available. Diphenylhydrazine is produced in several synthetic processes as an intermediate and a contaminant, but there is no way of estimating these substantial quantities.

II. EXPOSURE

A. Water

The highest reported concentration of 1,2-diphenylhydrazine in drinking water is one µg/l (U.S. EPA, 1975).

B. Food

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for diphenylhydrazine to be 29 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficient of diphenylhydrazine.

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C. Inhalation

Pertinent data could not be located in the available literature.

III. PHARMACOKINETICS

Pertinent information could not be located in the available literature regarding absorption, distribution and excretion.

A. Metabolism

Various metabolites, including the known carcinogen benzidine, have been identified in the urine of rats. 1,2-Diphenylhydrazine was administered orally (200,400 mg/kg), intraperitoneally (200 mg/kg), intratracheally (5,10 mg/kg) and intravenously (4,8 mg/kg). The metabolites detected were not dependent upon the base or route of administration (Williams, 1959).

IV. EFFECTS

A. Carcinogenicity

Diphenylhydrazine has been identified as producing significant increases in hepatocellular carcinoma at 5 µg/kg/day and 18.8 µg/kg/day in both sexes of rats; Zymbal's gland squamous-cell tumors in male rats at 18.8 µg/kg/day; neoplastic liver nodules in female rates at 7.5 µg/kg/day; and hepatocellular carcinomas in female mice at 3.75 µg/kg/day (NCI, 1978). Diphenylhydrazine was not carcinogenic in male mice.

B. Mutagenicity

No microbial mutagenetic assays with or without metabolic activation have been conducted on diphenylhydrazine. An intraperitoneal dose of 100 mg/kg had an inhibitory effect on the incorporation of (^{3}H)-thymidine into testicular DNA of experimental mice (Sieler, 1977).

C. Teratogenicity

Pertinent information could not be located in the available literature.

D. Toxicity

One study reported an LD_{50} of 959 mg/kg for male rats administered DPH as a five percent solution. In the Registry of Toxic Effects of Chemical Substances, the oral LD_{50} is listed as 301 mg/kg. Neoplasms resulted in rats after 52 weeks with a total dose of 16 g/kg DPH administered subcutaneously. In 2 mice studies, neoplasms resulted after 25 weeks with topical application of 5280 mg/kg and after 38 weeks with subcutaneous injection of 8400 mg/kg DPH. Liver and kidney damage have been implicated in the adverse effects of diphenylhydrazine chronically administered to rats. No experimental or epidemiological studies have been conducted on the effects of diphenylhydrazine in humans.

V. AQUATIC TOXICITY

A. Acute

Ninety-six-hour LC_{50} values for freshwater organisms have been reported as 270 µg/l for the bluegill, Lepomis macrochirus, and the 48-hour LC_{50} for the cladoceran, Daphnia magna, is 4,100 µg/l (U.S. EPA, 1978). No toxicity data for marine animals could be located in the available literature.

B. Chronic

A chronic value of 251 µg/l has been obtained for the freshwater cladoceran, Daphnia Magna (U.S. EPA, 1978). No chronic tests of diphenylhydrazine are available for marine organisms.

C. Plants

Pertinent data could not be located in the available literature.

D. Residues

Based on the octanol/water partition coefficient of 870 for 1,2-diphenylhydrazine, a bioconcentration factor of 100 has been estimated for aquatic organisms with a lipid content of 8 percent.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor aquatic criteria derived by U.S. EPA (1979), which are summarized below have gone through the process of public review; therefore, there is a possibility that these criteria may be changed.

A. Humans

No standards were found for humans exposed to diphenylhydrazine in occupational or ambient settings.

Recommended draft criteria for the protection of human health are as follows:

Exposure Assumptions	Risk Levels and Corresponding Criteria						
	0	10^{-7}		10^{-6}		10^{-5}	
2 liters of drinking water and consumption of 18.7 grams fish and shellfish (2)	0	4	ng/l	40	ng/l	400	ng/l
Consumption of fish and shellfish only.	0	.019	µg/l	0.19	µg	1.9	µg/l

B. Aquatic

Criterion to protect freshwater aquatic life from toxic effects of diphenylhydrazine have been drafted as a 24-hour average concentration of 17 µg/l and not to exceed 38 µg/l at any time.

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DIPHENYLHYDRAZINE

REFERENCES

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No. 97

Disulfoton

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISULFOTON

Summary

Disulfoton is a highly toxic organophosphorous insecticide used on many agricultural crops. The human oral LD_{Lo} is estimated at 5 mg/kg body weight. Exposure results in central nervous system toxicity. The LD_{50} for several animal species ranges from 3.2 to 6 mg/kg. Carcinogenic, mutagenic, and teratogenic studies were not found in the available literature. The occupational threshold limit value for disulfoton is 10 $\mu g/m^3$. Allowable residue tolerances for agricultural commodities range from 0.3 to 11.0 ppm.

Although disulfoton is considered toxic to aquatic organisms, specific studies on aquatic toxicity were not located in the available literature.

I. INTRODUCTION

Disulfoton is a highly toxic organophosphorous insecticide used in agriculture to control mainly sucking insects such as aphids and plantfeeding mites. Small amounts are used on home plants and gardens in the form of dry granules with low content of active ingredient (U.S. EPA, 1974). Disulfoton was introduced in 1956 by Bayer Leverkusen (Martin and Worthing, 1974), and today it is produced by only one U.S. manufacturer, Mobay Chemical Corporation, at its Chemogro Agricultural Division in Kansas City, Missouri (Stanford Research Institute (SRI), 1977). An estimated 4500 tonnes were produced in 1974 (SRI, 1977). Disulfoton is made by interaction of O,O-diethyl hydrogen phosphorodithioate and 2-(2-ethylthio)ethylchloride (Martin and Worthing, 1974). Disulfoton is slightly soluble in water and readily soluble in most organics. Its overall degradation constant is 0.02/day. Disulfoton has a bioconcentration factor of 1.91 and an octanol/water partition coefficient of 1.0 (see Table 1).

II. EXPOSURE

A. Water

Disulfoton concentrations are highest during the production process. Concentrated liquid wastes are barged to sea (150-200 mi; 240-320 km), and sludge wastes are disposed in landfills.

Agricultural application rates normally range from 0.25 to 1.0 lb/acre (0.28-1.1 kg/ha); to a maximum of 5.0 lb/acre (5.5 kg/ha) for some uses. Target crops include small grains, sorgum, corn, cotton, other field crops; some vegetable, fruit and nut crops; ornamentals (Fairchild, 1977).

Disulfoton is considered stable in groundwater. Less than 10 percent is estimated to decompose in five days (equivalent to 50-250 mi; 80-400

TABLE 1. PHYSICAL AND CHEMICAL PROPERTIES OF DISULFOTON

Synonyms: O,O-Diethyl S-(2-(ethylthio)ethyl) phosphorodithioate; O,O-Diethyl S-(2-(ethylthio)ethyl) dithiophosphate; Thiodemeton; Frumin; Glebofos; Ethylthiometon B; VUAgT 1964; Di-Syston G; Disipton; ENT-23437; Ethyl thiometon; VUAgT 1-4; Bay 19639; M 74 [pesticide]; Ekatin TD; CAS Reg. No. 298-04-4; M 74 (VAN); Bayer 19639; Di-Syston; Dithiodemeton; Dithiosystox; Solvirex; Frumin AL; Frumin G

Structural Formula: $(C_2H_5O)_2(P=S)SCH_2CH_2SC_2H_5$

Molecular Weight: 274.4

Description: Colorless oil; technical product is a dark yellowish oil; readily soluble in most organics

Specific Gravity and/or Density: $d_4^{20} = 1.144$

Melting and/or Boiling Points: bp 62°C at 0.01 mm Hg

Stability: Relatively stable to hydrolysis at pH below 8
Overall degradation rate constant (0.02/day)

Solubility (water): 25 ppm at room temp.

$$\frac{\text{sediment}}{H_2O} \cdot \frac{.5}{1}$$

Vapor Pressure: 1.8×10^{-4} mm Hg at 20°C

Bioconcentration Factor (BCF) and/or
Octanol/water partition coefficient (K_{ow}): $K_{ow} = 1.91$
BCF = 1.0

Source: Martin and Worthing, 1974; Fairchild, 1977; Windholz, 1976; U.S. EPA, 1980; Berg, et al. 1977.

km) in a river environment. Decomposition in a lake environment is estimated to be near 90 percent in one year (U.S. EPA 1980).

B. Food

In a study by Van Dyk and Krause (1978), disulfoton was applied as a granular formulation at 2 g/m length in rows during cabbage planting (5 percent active ingredients, rows one meter apart, plants 0.5 meters apart). The disulfoton sulphone concentration reached a maximum in 18 to 32 days and decreased to between 0.3 and 6.4 mg/kg 52 days after application. The cabbage residue of disulfoton at harvest time was below the maximum limit of 0.5 mg/kg.

Disulfoton applied at about 1.5 kg/10 cm-ha (hectare slice) persisted for the first week, and residue levels declined slowly the following week. After one month, only 20 percent of the amount applied was found. Disulfoton was not found to translocate into edible parts of lettuce, onions, and carrots (less than 5 ppb), but was present at about 20 ppb in the root system of lettuce (Belanger and Hamilton, 1979).

C. Inhalation and Dermal

Data are not available indicating the number of people subject to inhalation or dermal exposure to disulfoton. The primary human exposure would appear to occur during production and application. The U.S. EPA (1976) listed the frequency of illness, by occupational groups caused by exposure to organophosphorous pesticides. In 1157 reported cases, most illnesses occurred among ground applicators (229) and mixer/loaders (142); the lack of or refusal to use safety equipment, was a major factor of this contamination. Other groups affected were gardeners (101), field workers exposed to pesticide residues (117), nursery and greenhouse workers (75), soil fumigators in agriculture (29), equipment cleaners and mechanics (28), trac-

tor drivers and irrigators (23), workers exposed to pesticide drift (22), pilots (crop dusters) (17), and flaggers for aerial application (6). Most illnesses were a result of carelessness, lack of knowledge of the hazards, and/or lack of safety equipment. Under dry, hot conditions, workers tended not to wear protective clothing. Such conditions also tended to increase pesticide levels and dust on the crops.

III. PHARMACOKINETICS

A. Absorption, Distribution, and Excretion

Pertinent data could not be located in the available literature.

B. Metabolism

Disulfoton is metabolized in plants to sulfoxide and sulfone and the corresponding derivatives of the phosphorothioate and demeton-S. This is also the probable route in animals (Martin and Worthing, 1974; Menzie 1974; Fairchild, 1977).

IV. EFFECTS

A. Carcinogenicity, Mutagenicity and Teratogenicity

Pertinent data could not be located in the available literature.

B. Chronic Toxicity and Other Relevant Information

Disulfoton is highly toxic to all terrestrial and aquatic fauna. Human oral LD_{Lo} is estimated to be 5 mg disulfoton per kilogram body weight (5 mg/kg). The symptoms produced by sublethal doses are typical of central and peripheral nervous-system toxicity (Gleason, et al. 1969). The reported LD_{50} concentrations for other species are summarized below (Fairchild, 1977).

Species	Exposure Route	LD_{50} (mg/kg)
rat	oral	5
rat	dermal	6
rat	intraperitoneal	5.4
rat	intravenous	5.5
mouse	oral	5.5
mouse	intraperitoneal	7
bird	oral	3.2

Rats survived for 60 days at 0.5 mg/kg/day (Martin and Worthing 1974). The no-effect level in the diet was 2 ppm for rats and 1 ppm for dogs (Fairchild, 1977).

In rats, single injections of 1.2 mg disulfoton per kg body weight caused 14 percent reductions of hippocampal norepinephrine within 3 hours of exposure. Norepinephrine returned to control levels within 5 days (Holt and Hawkins, 1978). In female chicks administered with disulfoton intraperitoneally (single dose 8.6 mg/kg), the total lipid content of the sciatic nerve, kidney and skeletal muscles increased whereas that of the brain and spinal cord remained the same or decreased. When female chicks were orally administered with disulfoton (0.29 mg/kg daily for 71 days), the total lipid content in all the organs except the liver and sciatic nerves decreased. Although degenerative changes were indicated in both exposure studies, no adverse effect on the growth of chicks was noted (Gopel and Ahuja, 1979).

Disulfoton applied at 1 to 1.5 kg/ha very markedly decreased the populations of soil bacteria (Tiwari, et al. 1977).

V. AQUATIC TOXICITY

The 96-hour TL_m (equivalent to a 96-hour LC_{50}) for fathead minnows was found to be 2.6 mg/l in hard water and 3.7 mg/l in soft water.

Both tests were conducted at 25°C. The corresponding value for bluegills is estimated to be 0.07 mg/l (McKee and Wolf, 1963).

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The occupational threshold limit value for air has been established as 100 $\mu g/m^3$. Established residue tolerance for crops range from 0.3 to 12.0 ppm; 0.75 ppm for most (Fairchild, 1977).

B. Aquatic

Pertinent data could not be located in the available literature.

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No. 98

Endosulfan

Health and Environmental Effects

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ENDOSULFAN

Summary

Endosulfan is an insecticide and is a member of the organochlorocyclodiene insecticides. Endosulfan does not appear to be carcinogenic, mutagenic or teratogenic. In humans, chronic toxic effects have not been observed when endosulfan has been properly handled occupationally. Chronic feeding of endosulfan to rats and mice produced kidney damage, parathyroid hyperplasia, testicular atrophy, hydropic change of the liver, and lowered survival. Oral administration of endosulfan to pregnant rats increased fetal mortality and resorptions. Sterility can be induced in embryos in sprayed bird eggs. At very high levels of acute exposure, endosulfan is toxic to the central nervous system. The U.S. EPA has calculated an ADI of 0.28 mg based on a NOAEL of 0.4 mg/kg for mice in a chronic feeding study. The ADI established by the Food and Agricultural Organization (1975) and World Health Organization is 0.0075 mg/kg.

Ninety-six hour LC_{50} values ranged from 0.3 to 11.0 µg/l for five freshwater fish; from 0.09 to 0.6 µg/l for five saltwater fish in 48- or 96-hour tests; from 0.04 to 380 µg/l (EC_{50} and LC_{50}) for seven saltwater invertebrate species; and from 62 to 166 µg/l for Daphnia magna (48-hour LC_{50}). In the only chronic aquatic study involving endosulfan, no adverse effects on fathead minnows were observed at 0.20 µg/l.

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I. INTRODUCTION

Endosulfan (6,7,8,9,10,10-hexachloro-1,5,5a,6,9,9a-hexahydro-6,9-methano-2,4,3-benzodioxathiepin-3-oxide; $C_9Cl_6H_6O_3S$; molecular weight 406.95) is a light to dark brown crystalline solid with a terpene-like odor. Endosulfan is a broad spectrum insecticide of the group of polycyclic chlorinated hydrocarbons called cyclodiene insecticides. It also has uses as an acaricite. It has a vapor pressure of 9×10^{-3} mm Hg at 80 degrees centigrade. It exhibits a solubility in water of 60 to 150 µg/l and is readily soluble in organic solvents (U.S. EPA, 1979). The trade names of endosulfan include Beosit, Chlorithiepin, Cyclodan, Insectophene, Kop-Thiodan, Malix, Thifor, Thisnuml, Thioden, and Thionex (Berg, 1976).

Technical grade endosulfan has a purity of 95 percent and is composed of a mixture of two stereoisomers referred to as alpha-endosulfan and beta-endosulfan or I and II. These isomers are present in a ratio of 70 parts alpha-endosulfan to 30 parts beta-endosulfan. Impurities consist mainly of the degradation products and may not exceed 2 percent endosulfandiol and 1 percent endosulfan ether (U.S. EPA, 1979).

Production: three million pounds in 1974 (U.S. EPA, 1979).

Endosulfan is presently on the Environmental Protection Agency's restricted list. However, significant commercial use for insect control on vegetables, fruits, and tobacco continues (U.S. EPA, 1979).

Endosulfan is stable to sunlight but is susceptible to oxidation and the formation of endosulfan sulfate in the presence of growing vegetation (Cassil and Drummond, 1965). Endosulfan is readily adsorbed and absorbed by sediments (U.S. EPA, 1979). It is metabolically converted by microorganisms, plants, and animals to endosulfan sulfate, endosulfandiol, endosulfan ether, endosulfan hydroxyether and endosulfan lactone (Martens, 1976; Chopra

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and Mahfouz, 1977; Gorbach, et al. 1968; Miles and Moy, 1979). The end-product, endosulfan lactone, disappears quickly once formed. Accumulation of endosulfan sulfate may be favored in acidic soils (Miles and Moy, 1979).

II. EXPOSURE

A. Water

Endosulfan has been detected in water samples from some of the streams, rivers, and lakes in the United States and Canada and in Ontario municipal water supplies. The maximum concentration of endosulfan monitored in municipal water was 0.083 µg/l, which was found in Ontario municipal water samples but 68 µg/l has been measured in irrigation run-off (U.S. EPA, 1979). Endosulfan contamination of water results from agricultural runoff, industrial effluents, and spills. One serious accidental industrial discharge in Germany in 1969 caused a massive fishkill in the Rhine River. Most of the river water samples contained less than 500 ng/l endosulfan. Residues in run-off water from sprayed fields can be as high as 220 µg/l (U.S. EPA, 1979).

B. Food

An average daily intake (ADI) less than or equal to 0.001 mg of endosulfan and endosulfan sulfate was estimated for 1965-1970 from the market basket study of the FDA (Duggan and Corneliussen, 1972). The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for endosulfan to be 28 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on measured steady-state bioconcentration studies with mussels. The processing of leafy vegetables causes endosulfan residues to decline from 11 µg/kg to 6 µg/kg (Corneliussen, 1970).

C. Inhalation

In 1970, air samples from 16 states showed an average level of 13.0 ng/m^3 alpha-endosulfan and 0.2 ng/m^3 beta-endosulfan. None of the air samples collected in 1971 or 1972 contained detectable levels of either isomer (Lee, 1976). Endosulfan residues (endosulfan and endosulfan sulfate) have been detected in most types of U.S. tobacco products in recent years (U.S. EPA, 1979). Average residue levels range from 0.12 mg/kg to 0.83 mg/kg for 1971-1973 (Domanski, et al. 1973,1974; Dorough and Gibson, 1972). The extent to which endosulfan residues in tobacco products contribute to human exposure is not known. Spray operators can be exposed up to 50 µg/hour of endosulfan from a usual application of a 0.08 percent spray (Wolfe, et al. 1972). Non-target deposition on untreated plants after spraying may lead to residues of up to 679 µg/kg (Keil, 1972).

D. Dermal

Wolfe, et al. (1972) estimated that sprayers applying a 0.08 percent aqueous solution are exposed dermally to 0.6 to 98.3 mg/hour. Endosulfan can persist on the hands for 1 to 112 days after exposure (Kazen, et al. 1974).

III. PHARMACOKINETICS

A. Absorption

Undiluted endosulfan is slowly and incompletely absorbed from the mammalian gastointestinal tract, whereas endosulfan dissolved in cottonseed oil is readily though not completely absorbed (Boyd and Dobos, 1969; Maier-Bode, 1968). The beta-isomer is more readily absorbed than the alphaisomer. Alcohols, oils, and emulsifiers accelerate the absorption of endosulfan by the skin (Maier-Bode, 1968). Inhalation is not considered to be an important route of absorption for endosulfan except in spray operators (U.S. EPA, 1979).

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B. Distribution

After ingestion by experimental animals, endosulfan is first distributed to the liver and then to the other organs of the body and the remainder of the gastrointestinal tract (Boyd and Dobos, 1969; Maier-Bode, 1968). In cats, endosulfan levels peaked in brain, liver, spinal cord and plasma, with the brain and liver retaining the highest concentrations after administration of a 3 mg/kg dose (Khanna, et al. 1979).

In mice, 24 hours after oral administration of ^{14}C-endosulfan, residues were detected in fat, liver, kidney, brain, and blood (Deema, et al. 1966).

Data from autopsies of three suicides show levels of endosulfan in brain which were much lower than those in liver and kidney, which in turn, were lower than levels in blood (Coutselinis, et al. 1978). Data from another suicide indicate higher levels of endosulfan in liver and kidneys than in blood (Demeter, et al. 1977).

C. Metabolism

Endosulfan sulfate is the metabolite most commonly present in tissues, feces, and milk of mammals after administration of endosulfan (Whitacre, 1970; Demma, et al. 1966; FMC, 1963). The largest amounts of endosulfan sulfate are found in small intestine and visceral fat with only traces in skeletal muscle and kidney (Deema, et al. 1966). Endosulfan sulfate has been detected in the brains of two humans who committed suicide by ingesting endosulfan (Demeter and Heyndrickx, 1978), but not in the brains of mice given nonfatal doses of endosulfan. However, it has been detected in liver, visceral fat and small intestines of mice (Deema, et al. 1966). Other metabolites of endosulfan are endosulfan lactone, endosulfandiol, endosulfan hydroxyether, and endosulfan ether (Knowles, 1974; Menzie, 1974). These metabolites have also been found in microorganisms and plants (U.S. EPA, 1979).

D. Excretion

The principal route of excretion for endosulfan and endosulfan sulfate is in the feces (U.S. EPA, 1979). Other metabolites are also excreted in the feces and to a small extent in the urine, the metabolites in the latter being mainly in the form of endosulfan alcohol (U.S. EPA, 1979). In studies with sheep receiving a single oral dose of radiolabeled endosulfan, 92 percent of the dose was eliminated in 22 days. The organ with the highest concentration of radiolabeled endosulfan after 40 days was the liver. Major metabolites did not persist in the fat or in the organs (Gorbach, et al. 1968). After a single oral dose, the half-life of radiolabeled endosulfan in the feces and urine of sheep was approximately two days (Kloss, et al. 1966). Following 14 days of dietary exposure of female rats, the half-life of endosulfan residues was approximately seven days (Dorough, et al. 1978).

IV. EFFECTS

A. Carcinogenicity

In bioassays on both mice and rats, orally administered endosulfan was not carcinogenic even though doses were high enough to produce symptoms of toxicity (Kotin, et al. 1968; Innes, et al. 1969; Weisburger, et al. 1978).

B. Mutagenicity

Data from assays with Salmonella typhimurium (with and without microsomal activation) (Dorough, et al. 1978), Saccharomyces cerevisiae, Escherichia coli, and Serratia marcescens (Fahrig, 1974) indicate that endosulfan is not mutagenic.

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C. Teratogenicity

Endosulfan did not produce teratogenic effects in rats (Gupta, 1978).

D. Other Reproductive Effects

In rats, endosulfan produced dose-related increases in maternal toxicity and caused increases in fetal mortality and resorptions (Gupta, 1978). Doses of 100 mg/kg reduce hatchability of fertile white leghorn chicken eggs by 54 percent, but this was dependent on carrier (Dunachie and Fletcher, 1969). Alterations in the gonads of the embryos within sprayed hens' eggs were noted and the progeny of hens and quails, Coturnix Coturnix japonica, were sterile (U.S. EPA, 1979).

E. Chronic Toxicity

In the NCI bioassays (Kotin, et al. 1968; Weisberger, et al. 1978) endosulfan was toxic to the kidneys of rats of both sexes, and to the kidneys of male mice. Other signs of toxicity were parathyroid hyperplasia, testicular atrophy in male rats, and high early death rates in male mice.

In a two-year feeding study with rats (Hazelton Laboratories, 1959), endosulfan at 10 mg/kg diet reduced testis weight in males and lowered survival in females; at 100 mg/kg diet, renal tubular damage and some hydropic changes in the liver were induced.

In humans, there has been an absence of toxic effects with proper handling of endosulfan in the occupational setting (Hoechst, 1966).

F. Other Relevant Information

The acute toxicity of endosulfan sulfate is about the same as that of endosulfan. The LD_{50} for technical endosulfan in rats is ~ 22 to 46 mg/kg and 6.9 to 7.5 mg/kg in mice (Gupta, 1976). Reagent grade a- and β-endosulfan are less toxic to rats (76 and 240 mg/kg, respectively; Hoechst,

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1967). The inhalation 4-hour LC_{50} values for rats have been reported as 350 and 80 µg/l for males and females, respectively (Ely, et al. 1967). Acute toxicities of other metabolites (endosulfan lactone, endosulfandiol, endosulfan hydroxyether and endosulfan ether) are less than that of the parent compound (Dorough, et al. 1978).

At very high levels of acute exposure, endosulfan is toxic to the central nervous system (U.S. EPA, 1979). Endosulfan is a convulsant and causes fainting, tremors, mental confusion, irritability, difficulty in urination, loss of memory and impairment of visual-motor coordination. Acute intoxification can be relieved by diazepam but chronic effects are manifested in central nervous system disorders (Aleksandrowicz, 1979).

There appear to be sex differences (see previous Chronic Toxicity section) and species differences in sensitivity to endosulfan. Of the species tested with endosulfan, cattle are the most sensitive to the neurotoxic effects of endosulfan and appear to be closer in sensitivity to humans. Dermal toxicity of endosulfan-sprayed cattle is also high. Typical symptoms are listlessness, blind staggers, restlessness, hyperexcitability, muscular spasms, goose-stepping and convulsions (U.S. EPA, 1979).

Endosulfan is a nonspecific inducer of drug metabolizing enzymes (Agarwal, et al. 1978). Protein deficient rats are somewhat more susceptible to the toxic effects of endosulfan than controls (Boyd and Dobos, 1969; Boyd, et al. 1970).

V. AQUATIC TOXICITY

A. Acute Toxicity

Ninety-six hour LC_{50} values, using technical grade endosulfan, for five species of freshwater fish range from 0.3 µg/l for the rainbow trout, Salmo gairdneri, (Macek, et al. 1969) to 11.0 µg/l for carp finger-

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lings, Cyprinus carpio (Macek, et al. 1969; Schoettger, 1970; Ludemann and Neumann, 1960; Pickering and Henderson, 1966). Among freshwater invertebrates, Daphnia magna is reported to have 48-hour LC_{50} values ranging from 62 to 166 µg/l (Macek, et al. 1976; Schoettger, 1970), with three other invertebrates yielding 96-hour LC_{50} values of 2.3 (Sanders and Cope, 1968) to 107 µg/l (Sanders, 1969; Schoettger, 1970). Levels of 400 and 800 ng/l of technical endosulfan damaged the kidney, liver, stomach and intestine of Gymonocorymbus ternetzi. The 96-hour LC_{50} value was 1.6 µg/l (Amminikutty and Rege, 1977,1978).

Of the five saltwater fish species tested, the reported 48- or 96-hour LC_{50} values ranged from 0.09 (Schimmel, et al. 1977) to 0.6 µg/l (Butler, 1963,1964; Korn and Earnest, 1974; Schimmel, et al. 1977). The most sensitive species was the spot (Leiostomus xanthurus).

The seven saltwater invertebrate species tested showed a wide range of sensitivity to endosulfan. The range of EC_{50} and LC_{50} values is from 0.04 (Schimmel, et al. 1977) to 380 µg/l with the most sensitive species being the pink shrimp (Penaeus duorarum).

B. Chronic Toxicity

Macek, et al. (1976) provided the only aquatic chronic study involving endosulfan. No adverse effects on fathead minnow, Pimephales promelas, parents or offspring were observed at 0.20 µg/l. Gymonocorymbus ternetzi chronically exposed to 400 and 530 ng/l for 16 weeks evinced necrosis of intestinal mucosa cells, ruptured hepatic cells and destruction of pancreatic islet cells (Amminikutty and Rege, 1977,1978).

C. Plant Effects

Little data is available concerning the effects of endosulfan on aquatic micro/macrophytes. Growth of Chlorella vulgaris was inhibited > 2000 µg/l (Knauf and Schulze, 1973).

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D. Residues

Schimmel, et al. (1977) studied the uptake, depuration, and metabolism of endosulfan by the striped mullet, Mugil cephalus. When the concentrations of endosulfans I and II and endosulfan sulfate were combined to determine the bioconcentration factor (BCF), an average whole-body BCF of 1,597 was obtained. Nearly all the endosulfan was in the form of the sulfate. Even though the duration of the study was 28 days, this investigator questioned whether a steady-state condition was reached. Complete depuration occurred in just two days in an endosulfan-free environment. Residues in pond sediments may be as high as 50 µg/kg B-endosulfan and 70 µg/kg of endosulfan sulfate 280 days after insecticidal endosulfan application (FMC, 1971).

Dislodgable residues on cotton foliage in Arizona declined to 10 percent and one-third for the low-melting and high-melting isomers, respectively, 24 hours after application of 1.1 kg/ha endosulfan. However, though residues had declined to 4 percent and 11 percent respectively, 4 days after application endosulfan sulfate residues on the leaves increased markedly to 0.14 µg/cm^2 (Estesen, 1979).

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

The U.S. EPA (1979) has recommended a draft criterion for endosulfan in ambient water of 0.1 mg/l based on an ADI of 0.28 mg/day. This ADI was calculated from a NOAEL of 0.4 mg/kg obtained for mice in a chronic feeding study (Weisburger, et al. 1978) and an uncertainty factor of 100.

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The American Conference of Governmental Industrial Hygienists (ACGIH, 1977) TLV time weighted average for endosulfan is 0.1 mg/m^3. The tentative value for the TLV short-term exposure limit (15 minutes) is 0.3 mg/m^3.

The ADI for endosulfan established by the Food and Agricultural Organization and the World Health Organization is 7.5 µg/kg (FAO, 1975).

B. Aquatic

For endosulfan, the draft criterion to protect freshwater aquatic life is 0.042 µg/l in a 24-hour average and not to exceed 0.49 µg/l at any time. Saltwater criteria cannot be developed because of insufficient data (U.S. EPA, 1979).

ENDOSULFAN

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No. 99

Endrin

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

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ENDRIN

SUMMARY

Endrin does not appear to be carcinogenic. Endrin is teratogenic and embroytoxic in high doses and produces gross chromosomal abnormalities when administered intratesticularly. Chronic administration of endrin causes damage to the liver, lung, kidney, and heart of experimental animals. No information about chronic effects in humans is available. The ADI established by the Food and Agricultural Organization and World Health Organization is 0.002 mg/kg.

Endrin has proven to be extremely toxic to aquatic organisms. In general, marine fish are more sensitive to endrin with an arithmetic mean LC_{50} value of 0.73 µg/l, than freshwater fish with an arithmetic mean LC_{50} value of 4.42 µg/l. Invertebrate species tend to be more resistant than fish with arithmetic mean LC_{50} values of 3.80 and 58.91 µg/l for marine and freshwater invertebrates, respectively.

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ENDRIN

I. INTRODUCTION

Endrin (molecular weight 374) is a broad spectrum insecticide of the group of polycyclic chlorinated cyclodiene hydrocarbons of which the insecticides aldrin and dieldrin are also members. Endrin is isomeric with dieldrin and is used as a rodenticide and ovicide. The endrin sold in the U.S. is a technical grade product containing not less than 95 percent active ingredient. The solubility of endrin in water at 25°C is about 200 µg/l (U.S. EPA, 1979). Its vapor pressure is 2 x 10^{-7} mm Hg at 25°C (Martin, 1971).

Endrin is used primarily as an insecticide and also as a rodenticide and avicide. Over the past several years, endrin utilization has been increasingly restricted (U.S. EPA, 1979. Endrin production in 1978 was approximately 400,000 pounds (U.S. EPA, 1978). Endrin persists in the soil (U.S. EPA, 1979).

II. EXPOSURE

A. Water

Occasionally, groundwater may contain more than 0.1 µg/l. Levels as high as 3 µg/l have been correlated with precipitation and run off following endrin applications (U.S. EPA, 1978).

Concentrations of endrin in finished drinking water have been decreasing. In a study of ten municipal water treatment plants on the Mississippi or Missouri Rivers, the number of finished water samples containing concentrations of endrin exceeding 0.1 µg/l decreased from ten percent in 1964-

1965 to zero in 1966-1967 (Schafer, et al., 1969). The highest concentration of endrin in drinking water in New Orleans, Louisiana measured by the U.S. EPA in 1974 was 4 ng/l (U.S. EPA, 1974).

B. Food

The general population is rarely exposed to endrin through the diet. In the market basket study by the FDA, the total average daily intake from food ranged from approximately 0.009 µg/kg body weight in 1965 to 0.0005 µg/kg body weight in 1970 (Duggan and Lipscomb, 1969; Duggan and Corneliussen, 1972).

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor of endrin at 1,900 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on measured steady-state bioconcentration studies in six species (both freshwater and saltwater).

C. Inhalation

Exposure of the general population to endrin via the air decreased from a maximum level of 25.6 µg/m^3 in 1971 to a maximum level of 0.5 µg/m^3 in 1975 (U.S. EPA, 1979).

Tobacco products are contaminated with endrin residues. Average endrin residues for various types of tobacco products have been reported in the range of 0.05 µg/g to 0.2 µg/g (Bowery, et al., 1959; Domanski and Guthrie, 1974).

Inhalation exposure of users and manufacturers of endrin sprays may be around 10 µg/hour (Wolfe, et al. 1967) but use of dusts can produce levels as high as 0.41 mg/hour (Wolfe, et al. 1963).

D. Dermal

Dermal exposure of spray operators can range up to 3 mg/body/hour even for operators wearing standard protective clothing (Wolfe, et al. 1963, 1967). The spraying of dusts can lead to exposures of up to 19 mg/hour (Wolfe, et al. 1963).

III. PHARMACOKINETICS

A. Absorption

Endrin is known to be absorbed through the skin, lungs, and gut, but data on the rates of absorption are not available (U.S. EPA, 1979).

B. Distribution

Endrin is not stored in human tissues in significant quantities. Residues were not detected in plasma, adipose tissue, or urine of workers exposed to endrin (Hayes and Curley, 1968). Measurable levels of endrin have not been detected in human subcutaneous fat or blood, even in persons living in areas where endrin is used extensively (U.S. EPA, 1979). Endrin residues have been detected in the body tissues of humans only immediately after an acute exposure (U.S. EPA, 1979; Coble, et al. 1967).

In a 128 day study, dogs were fed 0.1 mg/endrin/kg body weight/day. Concentrations of endrin in the tissues at the end of the experiment were as follows: adipose tissue, 0.3 to 0.8 ug/g; heart, pancreas, and muscle, 0.3 ug/l; liver, kidney and lungs, 0.077 to 0.085 ug/g; blood, 0.002 to 0.008 ug/g (Richardson, et al., 1967). In a six month feeding study with dogs at endrin levels of 4 to 8 ppm in the

diet, concentrations of endrin were 1 µg/g in fat, 1 µg/g in liver, and 0.5 µg/g in kidney (Treon, et al., 1955).

C. Metabolism

In rats, endrin is readily metabolized in the liver and excreted as hydrophilic metabolites including hydroxyendrins, and 12-ketoendrin (also known as 9-ketoendrin). Hydroxyendrins and especially 12-ketoendrin have been reported to be more acutely toxic to mammals than the parent compound (Bedford, et al., 1975; Hutson, et al., 1975). The 12-ketoendrin is also more persistent in tissues. Female rats metabolize endrin more slowly than males (Jager, 1970).

D. Excretion

Endrin is one of the least persistent chlorinated hydrocarbon pesticides (U.S. EPA, 1979). Body content of endrin declines fairly rapidly after a single dose or when a continuous feeding experiment is terminated (Brooks, 1969). In rats, endrin and its metabolites are primarily excreted with the feces (Cole, et al., 1968; Jager, 1970). The major metabolite in rats is anti-12-hydroxyendrin which is excreted in bile as the glucuronide. 12-Ketoendrin was observed as a urinary metabolite in male rats; the major urinary metabolite in female rats is anti-12-hydroxyendrin-O-sulfate (Hutson, et al., 1975).

In rabbits, excretion is primarily urinary. In females, endrin excretion also occurs through the milk. Although endrin is rapidly eliminated from the body, some of its metabolites may persist for longer periods of time (U.S. EPA, 1979).

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IV. EFFECTS

A. Carcinogenicity

In lifetime feeding studies with Osborne-Mendel rats, endrin was neither tumorigenic nor carcinogenic (Deichmann, et al., 1970; Deichmann and MacDonald, 1971; Deichmann, 1972). A recent NCI bioassay concluded that endrin was not carcinogenic for Osborne-Mendel rats or for B6C3F1 mice (DHEW, 1979). However, a different conclusion has been reached by Reuber (1979) based only on one study (National Cancer Institute, 1977), compared with eight other inconclusive or unsatisfactory studies.

B. Mutagenicity

Endrin (1 mg/kg) administered intratesticularly caused chromosomal aberrations in germinal tissues of rats, including stickiness, bizarre configurations, and abnormal disjunction (Dikshith and Datta, 1972, 1973).

C. Teratogenicity

An increased incidence of club foot was found in fetuses of mice tnat had been treated with endrin (0.58 mg/kg) before becoming pregnant (Nodu, et al., 1972).

Treatment of pregnant hamsters with endrin (5 mg/kg) produced the following congenital abnormalities: open eye, webbed foot, cleft palate, fused ribs, and meningoencephalocele (Ottolenghi, et al., 1974; Chernoff, et al., 1979). Treatment of pregnant mice with endrin (2-5 mg/kg) produced open eye and cleft palate in the offspring (Ottolenghi, et al., 1974). Single doses which produced terato-

genic effects in hamsters and mice were one-half the LD_{50} in each species (Ottolenghi, et al., 1974).

D. Other Reproductive Effects

Endrin given to hamsters during gestation produced behavioral effects in both dams and offspring (Gray, et al., 1979). In another study endrin produced a high incidence of fetal death and growth retardation (Ottolenghi, et al., 1974).

E. Chronic Toxicity

Mammals appeared to be sensitive to the toxic effects of endrin at low levels in their diet. Significant mortality occurred in deer mice fed endrin at 2 mg/kg/day in the diet (Morris, 1968). The mice exhibited symptoms of CNS toxicity including convulsions. Lifetime feeding of endrin to rats at 12 mg/kg/day in the diet decreased viability and produced moderate increases in congestion and focal hemorrhages of the lung; slight enlargment, congestion and mottling of the liver, and slight enlargement, discoloration or congestion of the kidneys (Deichmann, et al., 1970). After 19 months on diets containing 3 mg/kg/day endrin, dogs had significantly enlarged kidneys and hearts (Treon, et al., 1955).

Chronic administration of relatively small doses of endrin to monkeys produced a characteristic change in the electroencephalogram (EEG); at higher doses, electrographic seizures developed. EEG and behavior were still abnormal three weeks after termination of endrin administration; sei-

zures recurred under stress conditions months after termination of endrin administration (Revin, 1968).

F. Other Relevant Information

Endrin is more toxic, in both acute and chronic studies, than other cyclodiene insecticides (U.S. EPA, 1979).

Female rats metabolize and eliminate endrin more slowly than males (Jager, 1970) and are more sensitive to endrin toxicity (U.S. EPA, 1979). Dogs and monkeys are more susceptible to endrin toxicity than other species (U.S. EPA, 1979).

Endrin, given in equitoxic doses with delnav, DDT, or parathion gave lower than expected LD_{50} values, suggestive of antagonism. Endrin given in equitoxic doses with aldrin (a closely related compound) or chlordane gave higher than expected LD_{50} values suggestive of synergism (Keplinger and Deichmann, 1967). Humans poisoned acutely exhibit convulsions, vomiting, abdominal pain, nausea, dizziness, mental confusion, muscle twitching and headache. Such symptoms have been elicited by doses as low as 0.2 mg/kg body weight. Any deaths have usually occurred through respiratory failure (Brooks, 1974).

V. AQUATIC TOXICITY

A. Acute

The toxic effects of endrin have been extensively studied in freshwater fish. LC_{50} values for static bioassays ranged from 0.046 µg/l for carp fry (Cyprinus carpio) fry to 140.00 µg/l for adult carp (Iyatomi, et al.,

1958). Excluding the results of age factor differences for this species, adjusted static LC_{50} values ranged from 0.27 µg/l for large mouth bass (Microptecus salmoides) (Fabacler, 1976) to 8.25 µg/l for the bluegill (Lepomis macrochirus) (Katz and Chadwick, 1961). The LC_{50} values for flow-through assays were 0.27 µg/l for the bluntnose minnow (Pimeplales notatus) to 2.00 µg/l for the bluegill (U.S. EPA, 1979). Twenty-five LC_{50} values for 17 species of freshwater invertebrates were reported, and ranged from 0.25 µg/l for stoneflies (Pteronarcys californica) to 500.0 µg/l for the snail, (Physa gyrina) (U.S. EPA, 1979).

For marine fish, LC_{50} values ranged from 0.005 µg/l for the Atlantic silversides (Menidia menidia) (Eisler, 1970) to 3.1 µg/l for the northern puffer (Sphaeroides maculatus). A total of 17 species were tested in 33 bioassays. The most sensitive marine invertebrate tested was the pink shrimp, (Penaeus duordrum) with an LC_{50} value of 0.037 µg/l, while the blue crab (Callinectes sapidus) was the most resistant, with an LC_{50} of 25 µg/l.

B. Chronic

Freshwater fish chronic values of 0.187 µg/l and 0.257 µg/l were reported for fathead minnows (Pimephales promelas) (Jarvinen and Tyo, 1978) and flagfish (Jordanella floridae) Hermanutz, 1978), respectively, in life cycle toxicity tests. No freshwater invertebrate species have been chronically examined. The marine fish, the sheepshead minnow (Cyprinodon variegatus) has provided a chronic value of 0.19 µg/l from embryolarval tests (Hansen, et al., 1977). The

grass shrimp (Palaemonetes pugio) must be exposed to less than a chronic concentration of 0.038 µg/l for reproductive success of this marine invertebrate species (TylerShroeder, in press).

C. Plants

Toxic effects were elicited at concentrations for freshwater algae ranging from 475 µg/l for Anacystis nidularas (Batterton, 1971) to >20,000 µg/l for Scenedesmus quadricauda and Oedogonium sp. Marine algae appeared more sensitive with effective concentration ranging from 0.2 µg/l for the algae, Agmenellum quadruplicatum (Batterton, 1978), to 1,000 µg/l for the algae Dunaliella tertiotecta (U.S. EPA, 1979).

D. Residues

Bioconcentration factors ranged from 140 to 222 in four species of freshwater algae. Bioconcentration factors ranging from 1,640 for the channel catfish Ictalurus punctatus (Argyle, et al. 1973) to 13,000 for the flagfish Jordanella floridae (Hermanutz, 1978) have been obtained. Among four marine species, bioconcentration factors ranging from 1,000 to 2,780 were observed for invertebrates and from 1,450 to 6,400 for marine fish. Residues as high as 0.5 ppm have been found in the mosquito fish, Gambusia affinis (Finley, et al. 1970) and fish frequently have contained levels above 0.3 ppm (Jackson, 1976).

VI. EXISTING GUIDELINES AND STANDARDS

Both the human health and aquatic criteria derived by U.S. EPA (1979), which are summarized below, have not gone

through the process of public review; therefore, there is a possibility that these criteria may be changed.

A. Human

The U.S. EPA (1979) has calculated an ADI for endrin of 70 µg from a NOAEL of 0.1 mg/kg for dogs in a 128 day feeding study and an uncertainity factor of 100. The U.S. EPA (1979) draft criterion of 1 µg/l for endrin in ambient water is based on the 1 µg/l maximum allowable concentration for endrin in drinking water proposed by the Public Health Service in 1965 (Schafer, et al., 1969) and on the calculations by EPA. Human exposure is assumed to come from drinking water and fish products only.

A maximum acceptable level of 0.002 mg/kg body weight/day (ADI) was established by the Food and Agricultural Organization (1973) and the World Health Organization.

A time weighted average TLV for endrin of 100 $\mu g/m^3$ has been established by OSHA (U.S. Code of Federal Regulations, 1972) and ACGIH (Yobs, et al., 1972).

The U.S. EPA (40 CFR Part 129.102) has promulgated a toxic pollutant effluent standard for endrin of 1.5 µg/l per average working day calculated over a period of one month, not to exceed 7.5 µg/l in any sample representing one working-day's effluent. In addition, discharge is not to exceed 0.0006 kg per 1,000 kg of production.

B. Aquatic

The draft criterion for the protection of freshwater aquatic life is 0.0020 µg/l as a 24 hour average concentration not to exceed 0.10 µg/l. For marine organisms, the draft criterion is 0.0047 µg/l as a 24 hour average not to exceed 0.031 µg/l.

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No. 100

Epichlorohydrin (1-chloro-2,3-epoxypropane)

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated epichlorohydrin and has found sufficient evidence to indicate that this compound is carcinogenic.

1-CHLORO-2,3-EPOXYPROPANE

(Epichlorohydrin)

Summary

The adverse health effects associated with exposure to epichlorohydrin are extreme irritation to the eyes, skin, and respiratory tract. Inhalation of vapor and percutaneous absorption of the liquid are the normal human routes of entry. Exposure to epichlorohydrin usually results from occupational contact with the chemical, especially in glycerol and epoxy resin operations. Pulmonary effects have been well documented. Recent studies have demonstrated epichlorohydrin to be a potent carcinogen to nasal tissue in experimental animals. Cytogenic studies both in vitro and in vivo in humans and experimental animals have indicated epichlorohydrin to be an active clastogenic agent. No data on the concentration of epichlorohydrin in drinking water or foods have been reported. Studies on the effects of epichlorohydrin to aquatic organisms could not be located in the available literature.

I. INTRODUCTION

This profile is based primarily on a comprehensive review compiled by Santodonato, et al. (1979). The health hazards of epichlorohydrin have also been reviewed by the National Institute for Occupational Safety and Health (NIOSH, 1976) and the Syracuse Research Corporation (SRC, 1979).

Epichlorohydrin (CH_2OCHCH_2Cl; molecular weight 92.53) is a colorless liquid at room temperature with a distinctive chloroform-type odor. The boiling point of epichlorohydrin is 116.4°C, and its vapor pressure is 20 mm Hg at 29°C. These factors contribute to the rapid evaporation of the chemical upon release into the environment.

Epichlorohydrin is a reactive molecule forming covalent bonds with biological macromolecules. It tends to react more readily with polarized groups, such as sulfhydryl groups.

The total U.S. production for epichlorohydrin was estimated at 345 million pounds in 1973 (Oesterhof, 1975), with 160 million pounds used as feedstock for the manufacture of glycerine and 180 million pounds used in the production of epoxy resins. Production levels for the year 1977 have been estimated at 400 million pounds.

II. EXPOSURE

A. Water

No ambient monitoring data on epichlorohydrin are available from which reliable conclusions on the potential exposure from drinking water may be made. However, if a major release of epichlorohydrin were realized, the chemical is stable enough to be transported significant distances. The rate of evaporative loss would give an estimated half-life of about two days for epichlorohydrin in surface waters (to a depth of 1m). The only reported contamination of a public water supply resulted from a tank car derailment

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and subsequent spillage of 20,000 gallons (197,000 pounds) of epichlorohydrin at Point Pleasant, West Virginia on January 23, 1978. Wells at the depth of 25 feet were heavily contaminated. More specific information is not yet available.

B. Food

Epichlorohydrin is used as a cross-link in molecular sieve resins, which are, in turn, used in the treatment of foods (21 CFR 173.40). Food starch may be etherified with epichlorohydrin, not to exceed 0 alone or in combination with propylene oxide, acetic anhyd cc anhydride (21 CFR 172.892). No data concerning concentrations of epichlorohydrin in foodstuffs has been generated.

C. Inhalation

Numerous environmental sources of epichlorohydrin have been identified (SRC, 1979). Epichlorohydrin is released into the atmosphere through waste ventilation processes from a number of industrial operations which result in volatilization of the chemical. No quantitative monitoring information is available on ambient epichlorohydrin concentrations. High concentrations have been observed in the immediate vicinity of a factory discharging epichlorohydrin into the atmosphere, but these were quickly despersed, with no detection of the chemical at distances greater than 600 M (Fomin, 1966).

III. PHARMACOKINETICS

A. Absorption

Absorption of epichlorohydrin in man and animals occurs via the respiratory and gastointestinal tracts, and by percutaneous absorption (U.S. EPA, 1979). Blood samples obtained from rats after 6 hours exposure to (^{14}C)epichlorohydrin at doses of 1 and 100 ppm in air revealed 0.46±0.19 and 27.8±4.7 µg epichlorohydrin per ml of plasma, respectively. The rates

epichlorohydrin per ml of plasma, respectively. The rates of uptake at these exposure levels were determined as 15.48 and 1394 ug per hour, and the dose received was 0.37 and 33.0 mg/kg (Smith, et al. 1979).

B. Distribution

The distribution of radioactivity in various tissues of rats fed (^{14}C)-epichlorohydrin has been examined (Weigel, et al. 1978). The chemical was rapidly absorbed with tissue saturation occurring within two hours in males and four hours in females. The kidney and liver accumulated the greatest amounts of radioactivity. Major routes of excretion were in the urine (38 to 40 percent), expired air (18 to 20 percent), and the feces (4 percent). The appearance of large amounts of $^{14}CO_2$ in expired air suggests a rapid and extensive metabolism of (^{14}C)-epichlorohydrin in rats.

C. Metabolism

Limited data concerning mammalian metabolism of epichlorohydrin suggest <u>in vivo</u> hydrolysis of the compound, yielding alpha-chlorohydrin (Jones, et al. 1969). Upon exposure to radioactively-labeled epichlorohydrin a small percentage of the radioactivity was expired as intact epichlorohydrin, while a large percentage of the radioactivity was excreted as $^{14}CO_2$, indicating a rapid and extensive metabolism of the (^{14}C)epichlorohydrin. Metabolites in the urine have been obtained by these researchers, but the final analysis as to the identity of the compounds is not yet complete. Van Duuren (1977) has suggested a metabolite pathway of epichlorohydrin to include glycidol, glycidaldehyde and epoxy-propionic acid.

D. Excretion

The percentages of total radioactivity recovered in the urine and expired air as $^{14}CO_2$ were 46 percent and 33 percent in the 1 ppm group, and 54 percent and 25 percent in the 100 ppm group, respectively. Rats

orally treated with 100 mg/kg excreted 51 percent of the administered epichlorohydrin in the urine and 38 percent in expired air, while 7 to 10 percent remained in the body 72 hours after exposure. Tissue accumulation of radioactivity was highest in kidneys and liver.

IV. EFFECTS

A. Carcinogenicity

Epichlorohydrin appears to have low carcinogenic activity following dermal application. In two studies, epichlorohydrin applied topically to shaved backs of rats or mice did not induce any significant occurrence of skin tumors (Weil, 1964; Van Duuren, et al. 1974). However, subcutaneous injection of epichlorohydrin at levels as low as 0.5 mg have resulted in the induction of tumors at the injection site.

Extensive inhalation studies have recently identified epichlorohydrin as a potent nasal carcinogen in rats. At concentrations of 100 ppm, significant increases in the occurrence of squamous cell carcinomas of the nasal turbinates have been observed. Such tumors have been reported in lifetime exposure studies at 30 ppm but not at 10 ppm (Nelson, 1977, 1978).

Several recent epidemiological studies have suggested the risk of cancer as a result of occupational epichlorohydrin exposure. Both respiratory cancers and leukemia are in excess among some exposed worker populations, but this increase was not shown to be statistically significant (Enterline and Henderson, 1978; Enterline, 1979). The data suggest a latency period of roughly 15 years before the onset of carcinogenic symptoms. A second survey has failed to substantiate these findings (Shellenberger, et al. 1979). However, this survey used a younger study population with less exposure to epichlorohydrin.

B. Mutagenicity

Epichlorohydrin has been shown to cause reverse mutations in several organisms (SRC, 1979).

Cytogenetic studies with experimental animals have revealed increased aberrations in animals treated with epichlorohydrin. Both mice and rats have displayed dose-dependent increases in abnormal chromosome morphology at exposure levels ranging from 1 to 50 mg/kg (Santodonato, et al. 1979).

In humans, the clastogenic properties of epichlorohydrin have been reported in workers occupationally exposed to the chemical and in cultured "normal" lymphocytes exposed to epichlorohydrin (SRC, 1979). Cytogenetic evaluation of exposed workers has shown an increase of somatic cell chromosome aberrations associated with concentrations ranging from 0.5 to 5.0 ppm (2.0 to 20 mg/m^3) (SRC, 1979). Such chromosomal damage appears to be reversible once exposure to the chemical ceases.

C. Teratogenicity

Pregnant rats and rabbits exposed to 2.5 to 25 ppm epichlorohydrin during days 6 to 15 or days 6 to 18 of gestation showed a mild teratogenic response (John, et al. 1979). However examinations of all fetal tissue have not been completed. The incidence of resorbed fetuses was not altered by exposure to epichlorohydrin at the doses employed.

D. Other Reproductive Effects

The antifertility properties of epichlorohydrin have been examined by several investigators. Administration of 15 mg/kg/day of epichlorohydrin for 12 days resulted in reduced fertility of male rats (Halen, 1970). Five repeated doses of 20 mg/kg were more effective in rendering male rats infertile than was one 100 mg/kg dose or five 50 mg/kg doses (Cooper, et al.

1974). The suggested mode of action of epichlorohydrin is via the *in vivo* hydrolysis of the compound which produces alpha-chlorohydrin. Altered reproductive function has been reported for workers occupationally exposed to epichlorohydrin at concentrations less than 5 ppm.

E. Chronic Effects

Two species of rats and one specie of mice (both sexes) were exposed to 5 to 50 ppm epichlorohydrin for six hours per day, five days per week for a total of 65 exposures. All species and sexes displayed inflammatory and degenerative changes in nasal tissue, moderate to severe tubular nephrosis, and gross liver pathology at 50 ppm exposure (Quast, et al. 1979a). The same research group has also examined the effect of 100 ppm exposure for 12 consecutive days. The toxicity to nasal tissues was similar (Quast, et al. 1979b).

Altered blood parameters (e.g. increased neutrophilic megamyelocytes, decreased hemoglobin, hematocrit, and erythrocytes) have been observed in rats exposed to 0.00955 to 0.04774 ml epichlorohydrin per kg body weight administered intraperitoneally (Lawrence, et al. 1972). Lesions of the lungs and reduced weight gains were also observed.

Toxicity studies with various animal species have established that epichlorohydrin is moderately toxic by systemic absorption (Lawrence, et al. 1972). Acute oral LD_{50} values in experimental animals have ranged from 155 to 238 mg/kg for the mouse and from 90 to 260 mg/kg in the rat. Inhalation LC_{50} values range from 360 to 635 ppm in rats, to 800 ppm in mice (SRC, 1979). Single subcutaneous injections of epichlorohydrin in rats at doses of 150 or 180 mg/kg have resulted in severe injury to the kidney (Rotara and Pallade, 1966).

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Accidental human exposures have been reviewed (NIOSH, 1976; Santodonato, et al. 1979). Direct exposure to epichlorohydrin vapor results in severe irritation of the eyes and respiratory membranes, followed by nausea, vomiting, headache, dyspnea, and altered liver function. A significant decrease was reported in pulmonary function among workers exposed to epichlorohydrin in an epoxy-resin manufacturing process. Workers were simultaneously exposed to dimethyl amino propylamine.

V. AQUATIC TOXICITY

Pertinent data could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

Existing occupational standards for exposure to epichlorohydrin are reviewed in the NIOSH (1976) criteria document. The NIOSH recommended environmental exposure limit is a 2 mg/m^3 10-hour time-weighted average and a 19 mg/m^3 15-minute ceiling concentration. The current Occupational Safety and Health Administration standard is an 8-hour time-weighted average concentration of 5 ppm (20 mg/m^3).

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1-CHLORO-2,3-EPOXYPROPANE(EPICHLOROHYDRIN)

REFERENCES

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No. 101

Ethyl Methacrylate

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

ETHYL METHACRYLATE

Summary

Information on the carcinogenic and mutagenic effects of ethyl methacrylate was not found in the available literature. Ethyl methacrylate has, however, been shown to cause teratogenic effects in rats.

Chronic occupational exposure to ethyl methacrylate has not been reported in the available literature.

Data concerning the effects of ethyl methacrylate on aquatic organisms were not found in the available literature.

ETHYL METHACRYLATE

I. INTRODUCTION

Ethyl methacrylate (molecular weight 114.15) is the ethyl ester of methacrylic acid. It is a crystalline solid that melts at less than 75°C, has a boiling point of 117°C, a density of 0.9135, and an index of refraction of 1.4147. It is insoluble in water at 25°C and is infinitely soluble in alcohol and ether (Weast, 1975). It possesses a characteristic unpleasant odor (Austian, 1975).

Widely known as "Plexiglass" (in the polymer form), ethyl methacrylate is used to make polymers, which in turn are used for building, automotive, aerospace, and furniture industries. It is also used by dentists as dental plates, artificial teeth, and orthopedic cement (Austian, 1975).

II. EXPOSURE

Ethyl methacrylate is used in large quantities and therefore has potential for industrial release and environmental contamination. Ethyl methacrylate in the polymerized form is not toxic; however, chemicals used to produce ethyl methacrylate are extremely toxic. No monitoring data are available to indicate ambient air or water levels of the compound.

Human exposure to ethyl methacrylate from foods cannot be assessed due to a lack of monitoring data.

Bioaccumulation data on ethyl methacrylate were not found in the available literature.

III. PHARMACOKINETICS

Specific information on the metabolism, distribution, absorption, or elimination of ethyl methacrylate was not found in the available literature.

No evidence has been found of the presence of ethyl methacrylate in the human urine. Therefore, it is hypothesized that it is rapidly metabolized and undergoes complete oxidation (Austian, 1975).

IV. EFFECTS

A. Carcinogenicity and Mutagenicity

Information on the carcinogenic and mutagenic effects of ethyl methacrylate was not found in the available literature.

B. Teratogenicity

Ethyl methacrylate is teratogenic in rats. Female rats were given intraperitoneal injections of 0.12 mg/kg, 0.24 mg/kg, and 0.41 mg/kg, on days 5, 10, and 15 of gestation. These doses were 10, 20, and 33 percent, respectively, of the acute intraperitoneal LD_{50} dose. Animals were sacrificed one day before parturition (day 20).

Deleterious effects were observed in the developing embryo and fetus. Effects were compound and generally dose-related. A 0.1223 ml/kg injected dose resulted in unspecified gross abnormalities and skeletal abnormalities in 6.3 percent and 5.0 percent of the test animals, respectively, when compared to the untreated controls. A dose of 0.476 ml/kg resulted in gross abnormalities in 15.7 percent of the treated animals and skeletal abnormalities in 11.7 percent of the treated animals (Singh, et al. 1972).

C. Other Reproductive Effects and Chronic Toxicity

Information on other reproductive effects and chronic toxicity of ethyl methacrylate was not found in the available literature.

D. Acute Toxicity

Lower molecular weight acrylic monomers such as ethyl methacrylate cause systemic toxic effects. Its administration results in an immediate

increase in respiration rate, followed by a decrease after 15-40 minutes. A prompt fall in blood pressure also occurs, followed by recovery in 4-5 minutes. As the animal approaches death, respiration becomes labored and irregular, lacrimation may occur, defecation and urination increase, and finally reflex activity ceases, and the animal lapses into a coma and dies (Austian, 1975).

Acrylic monomers are irritants to the skin and mucous membranes. When placed in the eyes of animals, they elicit a very severe response and, if not washed out, can cause permanent damage (Austian, 1975).

As early as 1941, Deichmann demonstrated that injection of 0.03 cc/kg body weight ethyl methacrylate caused a prompt and sudden fall in blood pessure, while respiration was stimulated immediately and remained at this level for 30 minutes. The final lethal dose (0.90-.12 cc/kg) brought about respiratory failure, although the hearts of these animals were still beating (Deichmann, 1941).

Work by Mir, et al. (1974) demonstrated that respiratory system effects alone may not kill the animal, but that cardiac effects may also contribute to the cause of death (Austian, 1975). Twelve methacrylate esters and methacrylic acid were tested on isolated perfused rabbit heart. Concentrations as low as 1 part in 100,000 (v/v) produced significant effects. The effects were divided into three groups according to the reversibility of the heart response. Ethyl methacrylate was placed in "Group 1", in which the heart response is irreversible at all concentrations (1:100,000; 1:10,000; 1:1,000). Five percent (v/v) caused a 41.2 percent decrease in the heart rate of isolated rabbit heart. The same concentration reduced heart contraction by 64 percent and coronary flow by 61.5 percent (Austian, 1975).

The findings of Deichmann (1941) that ethyl methacrylate affects blood pressure and respiration is substantiated by studies of Austian (1975). Response following administration of ethyl methacrylate was characterized by a biphenic response, an abrupt fall in blood pressure followed by a more sustained rise. Austian (1975) also found that the respiration rate is increased, the duration of effect being approximately 20 minutes, after which time the respiration rate returned to normal.

In the available literature LD_{50} values were found for only rabbit and rat; these were established by Deichmann in 1941. The oral value for the rat is 15,000 mg/kg, as opposed to 3,654-5,481 mg/kg for the rabbit. Inhalation values for the rat have been reported to be 3,300 ppm for 8 hours (Patty, 1962). Deichmann also established a skin toxicity LD_{50} for rabbit which was greater than 10 ml/kg. This was substantiated by another test which showed that moderate skin irritation (in rabbits) does result from ethyl methacrylate exposure (Patty, 1962).

VI. EXISTING GUIDELINES AND STANDARDS

Information on existing guidelines and standards was not found in the available literature.

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ETHYL METHACRYLATE

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No. 102

Ferric Cyanide

Health and Environmental Effects

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DISCLAIMER

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FERRIC CYANIDE

I. INTRODUCTION

Ferric cyanide is a misnomer and is not listed as a specific compound in the comprehensive compendia of inorganic compounds (Weast, 1978). There are, however, a class of compounds known as "iron cyanide blues" consisting of various salts where the anions are the ferricyanide, $[Fe(CN)_6]^{3-}$, or the ferrocyanide, $[Fe(CN)_6]^{4-}$, and the cations are either Fe(III) or Fe(II) and sometimes mixtures of Fe(II) and potassium (Kirk and Othmer, 1967). The empirical formula of the misnamed ferric cyanide, $Fe(CN)_3$, corresponds actually to one of the ferricyanide compounds, the ferric ferricyanide with the actual formula $Fe[Fe(CN)_6]$, also known as Berlin green. The acid from which these salts are derived is called ferricyanic acid, $H_3[Fe(CN)_6]$ (also known as hexacyanoferric acid), molecular weight 214.98, exists as green-blue deliquescent needles, decomposes upon heating, and is soluble in water and alcohol. In this EPA/ECAO Hazard Profile only ferric ferricyanide, $Fe[Fe(CN)_6]$, and ferric ferrocyanide, $Fe_4[Fe(CN)_6]_3$, are considered; other ferrocyanide compounds are reported in a separate EPA/ECAO Hazard Profile (U.S. EPA, 1980).

These compounds are colored pigments, insoluble in water or weak acids, although they can form colloidal dispersions in aqueous media. These pigments are generally used in paint, printing inks, carbon paper inks, crayons, linoleum, paper pulp, writing inks and laundry blues. These compounds are sensitive to alkaline decomposition (Kirk and Othmer, 1967).

II. EXPOSURE

Exposure to these compounds may occur occupationally or through ingestion of processed food or contaminated water. However, the extent of food or water contamination from these compounds has not been described in the

available literature. Prussian blue, potassium ferric hexacyanoferrate (II), has been reported as an antidote against thallium toxicity. When administered at a dose of 10 g twice daily by duodenal intubation, it prevents the intestinal reabsorption of thallium (Dreisbach, 1977).

III. PHARMACOKINETICS

A. Absorption and Distribution

Pertinent data could not be located in the available literature.

B. Metabolism

There is no apparent metabolic alteration of these compounds. As for the other ferrocyanide and ferricyanide salts, these compounds are not cyanogenic (Gosselin, et al. 1976).

C. Excretion

No information is available for ferric hexacyanoferrates (II) or (III), but information is available for other related ferrocyanide and ferricyanide salts (U.S. EPA, 1980; Gosselin, et al. 1976) which seems to be rapidly excreted in urine apparently without metabolic alteration.

IV. EFFECTS

A. Carcinogenicity, Mutagenicity, Teratogenicity, Chronic Toxicity, and Other Reproductive Effects

Pertinent data could not be located in the available literature.

B. Acute Toxicity

No adequate toxicity data are available. All ferrocyanide and ferricyanide salts are reported as possibly moderately toxic (from 0.5 to 5.0 mg/kg as a probable lethal dose in humans) (Gosselin, et al. 1976).

V. AQUATIC TOXICITY

Pertinent data could not be located in the available literature regarding the aquatic toxicity of ferric cyanide.

VI. EXISTING GUIDELINES AND STANDARDS

Pertinent data could not be located in the available literature.

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No. 103

Fluoranthene

Health and Environmental Effects

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FLUORANTHENE

SUMMARY

No direct carcinogenic effects have been produced by fluoranthene after administration to mice. The compound has also failed to show activity as a tumor initiator or promoter. However, it has shown cocarcinogenic effects on the skin of mice when combined with benzo(a)pyrene, increasing tumor incidence and decreasing tumor latency.

Fluoranthene has not shown mutagenic, teratogenic or adverse reproductive effects.

Daphnia magna appears to have low sensitivity to fluoranthene with a reported 48-hour EC_{50} of 325,000 µg/1. The bluegill, however, is considerably more sensitive with an observed 96-hour LC_{50} value of 3,980. The 96-hour LC_{50} for mysid shrimp is 16 µg/1, and a reported chronic value is 16 µg/1. Observed 96-hour EC_{50} values based on cell numbers for fresh and saltwater algae are over 45,000 µg/1.

FLUORANTHENE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Fluoranthene (U.S. EPA, 1979).

Fluoranthene (1,2-benzacenapthene, M.W. 202) is a polynuclear aromatic hydrocarbon of molecular formula $C_{16}H_{10}$. Its physical properties include: melting point, 111°C; boiling point, 375°C; water solubility, 265 µg/l (U.S. EPA, 1978).

Fluoranthene is chemically stable, but may be removed from water by biodegradation processes (U.S. EPA, 1979). The compound is relatively insoluble in aqueous systems. Fluoranthene may be adsorbed and concentrated on a variety of particulate matter. Micelle formation through the action of organic solvents or detergents may occur. (U.S. EPA, 1979).

Flouranthene is produced from the pyrolytic processing of coal and petroleum and may result from natural biosynthesis (U.S. EPA, 1979).

II. EXPOSURE

Fluoranthene is ubiquitous in the environment; it has been monitored in food, water, air, and in cigarette smoke (U.S. EPA, 1979). Sources of contamination include industrial effluents and emissions, sewage, soil infiltration, and road runoff (U.S. EPA, 1979). Monitoring of drinking water has shown an average fluoranthene concentration of 27.5 ng/l in positive samples (Basu, et al. 1978). Food

levels of the compound are in the ppb range, and will increase in smoked or cooked foods (pyrolysis of fats) (U.S. EPA, 1979). Borneff (1977) has estimated that dietary intake of fluoranthene occurs mainly from fruits, vegetables, and bread.

An estimated daily exposure to fluoranthene has been prepared by EPA (1979):

Source	Estimated Exposure
Water	0.017 µg/day
Food	1.6 - 16 µg/day
Air	0.040 - 0.080 µg/day

Based on the octanol/water partition coefficient, the U.S. EPA (1979) has estimated weighted average bioconcentration factor of 890 for fluoranthene for the edible portion of fish and shellfish consumed by Americans.

III. PHARMACOKINETICS

A. Absorption

Based on animal toxicity data (Smythe, et al. 1962), fluoranthene seems well absorbed following oral or dermal administration. The related polynuclear aromatic hydrocarbon (PAH), benzo(a)pyrene, is readily absorbed across the lungs (Vainio, et al. 1976).

B. Distribution

Pertinent information could not be located in the available literature. Experiments with benzo(a)pyrene indicate localization in a wide variety of body tissues, primarily in body fats (U.S. EPA, 1979).

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C. Metabolism

Pertinent information could not be located in the available literature. By analogy with other PAH compounds, fluoranthene may be expected to undergo metabolism by the mixed function oxidase enzyme complex. Transformation products produced by this action include ring hydroxylated products (following epoxide intermediate formation) and conjugated forms of these hydroxylated products (U.S. EPA, 1979).

D. Excretion

Pertinent information could not be located in the available literature. Experiments with PAH compounds indicate excretion through the hepatobiliary system and the feces; urinary excretion varies with the degree of formation of conjugated metabolites (U.S. EPA, 1979).

IV. EFFECTS

A. Carcinogenicity

Testing of fluoranthene in a marine carcinogenesis bioassay failed to show tumor production following dermal or subcutaneous administration of fluoranthene (Barry, et al., 1935).

Skin testing of fluoranthene as a tumor promoter or initiator in mice has also failed to show activity of the compound (Hoffman, et al., 1972; Van Duuren and Goldschmidt, 1976).

Fluoranthene has been demonstrated to have carcinogenic activity (Hoffmann and Wynder, 1963; Van Duuren

and Goldschmidt, 1976). The combination of fluoranthene and benzo(a)pyrene produced an increased number of papillomas and carcinomas, with shortened latency period (Van Duuren and Goldschmidt, 1976).

B. Mutagenicity

Fluoranthene failed to show mutagenic activity in the Ames Salmonella assay in the presence of enzyme activation mix (Tokiwa, et al. 1977; La Voie, et al. 1979).

C. Teratogenicity

Pertinent information could not be located in the available literature. Certain PAH compounds (7,12-dimethylbenz(a)anthracene and derivatives) have been shown to produce teratogenic effects in the rat (Currie, et al. 1970; Bird, et al. 1970).

D. Other Reproductive Effects

Pertinent information could not be located in the available literature.

E. Chronic Toxicity

Pertinent information could not be located in the available literature.

V. AQUATIC TOXICITY

A. Acute Toxicity

The 96-hour LC_{50} value for the bluegill, Lepomis macrochirus, is reported to be 3,980 µg/l (U.S. EPA, 1978). The sheepshead minnow, Cyprinodon variegatus, was exposed to concentrations of fluoranthene as high as 560,000 µg/l with no observed LC_{50} value (U.S. EPA, 1978). The fresh-

water invertebrate Daphnia magna appears to have a low sensitivity to fluoranthene with a reported 48-hour EC_{50} value of 325,000 µg/l. The 96-hour LC_{50} value for the salt-water mysid shrimp, Mysidopsis bahia, is 16 µg/l.

B. Chronic Toxicity

There are no chronic toxicity data presented on exposure of fluoranthene to freshwater species. A chronic value for the mysid shrimp is 16 µg/l.

C. Plant Effects

The freshwater alga, Selenastrum capricornutum, when exposed to fluoranthene resulted in a 96-hour EC_{50} value for cell number of 54,400 µg/l. On the same criterion, the 96-hour EC_{50} value for the marine alga, Skeletonema costatum, is 45,600 µg/l (U.S. EPA, 1979).

D. Residues

No measured steady-state bioconcentration factor (BCF) is available for fluoranthene. A BCF of 3,100 can be estimated using the octanol/water partition coefficient of 79,000.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The World Health Organization (1970) has established a recommended standard of 0.2 µg/l for all PAH compounds in drinking water.

Based on the no-effect level determined in a single animal study (Hoffman, et al. 1972), the U.S. EPA (1979) has estimated a draft ambient water criterion of 200 µg/l for fluoranthene. However, the lower level derived for

total PAH compounds is expected to have precedence for fluoranthene.

B. Aquatic

For fluoranthene, the draft criterion to protect freshwater aquatic life is 250 µg/l as a 24-hour average, not to exceed 560 µg/l at any time. For saltwater life, the criterion is 0.30 µg/l as a 24-hour average, not to exceed 0.69 µg/l at any time.

FLUORANTHENE

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No. 104

Formaldehyde

Health and Environmental Effects

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FORMALDEHYDE

SUMMARY

The major source of formaldehyde contamination in the environment is combustion processes, especially automobile emissions. Formaldehyde is a recognized component of photochemical smog. A recent source of concern is the release of formaldehyde from resins used in home construction and insulation.

Bioaccumulation of formaldehyde is considered unlikely due to its high chemical reactivity. Formaldehyde rapidly degrades in the atmosphere by photochemical processes; however, it can also be formed by the photochemical oxidation of atmospheric hydrocarbons.

Formaldehyde is rapidly absorbed via the lungs or gut; following absorption into the blood, however, formaldehyde disappears rapidly due to reactions with tissue components and because of its metabolism.

The U.S. EPA's Carcinogen Assessment Group recently concluded that "there is substantial evidence that formaldehyde is likely to be a human carcinogen." This finding was based on preliminary results from a chronic inhalation study of formaldehyde which reported carcinomas of the nasal cavity in 3 rats after 16 months of exposure. This type of tumor is extremely rare is unexposed rats of the strain used in the study.

There is an extensive data base showing that formaldehyde is mutagenic in microorganisms, plants, insects, cultured mammalian cells, and mice. It was negative in a teratogenicity assay. Formaldehyde is known to be a mucous membrane irritant in humans;

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it is also known to be an allergen in sensitive individuals.

I. INTRODUCTION

This profile is based on a U.S. EPA report entitled "Investigation of Selected Potential Environmental Contaminants: Formaldehyde" (1976) and other selected references.

Formaldehyde (HCHO; molecular weight 30.03) is a colorless gas having a pungent odor and an irritating effect on mucous membranes. It has the following physical/chemical properties (U.S. EPA, 1976; Windholz, 1976):

Boiling Point:	-19.2°C
Melting Point:	-92°C
Density in Air:	1.067
Solubility:	soluble in water and many organic solvents.

A review of the production range (includes importation) statistics for formaldehyde (CAS No. 50-00-0) which is listed in the initial TSCA Inventory (1979a) has shown that between 2 billion and 7 billion pounds of this chemical were produced/imported in 1977.*/

Formaldehyde is usually sold as an aqueous solution containing 37% formaldehyde by weight; it is also available as a linear

*/ This production range information does not include any production/importation data claimed as confidential by the person(s) reporting for the TSCA Inventory, nor does it include any information which would compromise Confidential Business Information. The data submitted for the TSCA Inventory, including production range information, are subject to the limitations contained in the Inventory Reporting Regulations (40 CFR 710).

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polymer known as paraformaldehyde and a cyclic trimer known as trioxane. Formaldehyde is used in the production of urea-formaldehyde resins, phenol-formaldehyde resins, polyacetal resins, various other resins, and as an intermediate in the production of a variety of chemicals. Manufacture of resins consumes over 50% of annual domestic formaldehyde production. Urea-formaldehyde and phenol-formaldehyde resins are used as adhesives for particle board and plywood, and in making foam insulation. Polyacetal resins are used to mold a large variety of plastic parts for automobiles, appliances, hardware, and so on (U.S. EPA, 1976).

II. EXPOSURE

NIOSH (1976) estimates that 1,750,000 workers are potentially exposed to formaldehyde in the workplace.

A. Environmental Fate

Formaldehyde and nascent forms of formaldehyde can undergo several types of reactions in the environment including depolymerization, oxidation-reduction, and reactions with other atmospheric and aquatic pollutants. Formaldehyde can react photochemically in the atmosphere to form H and HCO radicals; once formed, these radicals can undergo a wide variety of atmospheric reactions (U.S. EPA, 1976). Hydrogen peroxide can also be formed during photodecomposition of formaldehyde (Purcell and Cohen, 1967; Bufalini et al., 1972). The atmospheric half-life of formaldehyde is less than one hour in sunlight (Bufalini et al., 1972).

Even though formaldehyde is often used as a bacteriocide, there are some microorganisms which can degrade the chemical (U.S. EPA, 1976). Kamata (1966) studied biological degradation of formaldehyde in lake water. Under aerobic conditions in the laboratory, known quantities of formaldehyde were decomposed in about 30 hours at 20°C; anaerobic decomposition took about 48 hours. No decomposition was noted in sterilized lake water.

Paraformaldehyde slowly hydrolyzes and depolymerizes as it dissolves in water to yield aqueous formaldehyde. Trioxane has more chemical and thermal stability; it is inert under aqueous neutral or alkaline conditions. In dilute acid solutions, it slowly depolymerizes (U.S. EPA, 1976).

B. Bioconcentration

Formaldehyde is a natural metabolic product and does not bioconcentrate (U.S. EPA, 1976).

C. Environmental Occurrence

Environmental contamination from formaldehyde manufacture and industrial use is small and localized compared with other sources. Combustion and incineration processes comprise the major sources of formaldehyde emissions. Stationary sources of formaldehyde emissions include power plants, manufacturing facilities, home consumption of fuels, incinerators, and petroleum refineries. Mobile sources of formaldehyde emissions include automobiles, diesels, and aircraft. The automobile, however,, is the largest source of formaldehyde pollution. It is estimated that over 800 million pounds of formaldehyde were released to the air in the United States in 1975; of this amount, over 600

million pounds are estimated to result from the use of automobiles. In addition to formaldehyde, automobile exhaust also contains large quantities of hydrocarbons. Through photochemical processes in the atmosphere, these hydrocarbons are oxidized to formaldehyde, among other things, further adding to the environmental load of formaldehyde (U.S. EPA, 1976).

Urea-formaldehyde foam insulation has been implicated as a source of formaldehyde fumes in homes insulated with this material. Wood laminates (plywood, chip board, and particle board) commonly used in the construction of mobile homes are also known to release formaldehyde vapors into the home atmosphere (U.S. EPA, 1979b).

III. PHARMACOKINETICS

A. Absorption

Under normal conditions formaldehyde can enter the body through dermal and occular contact, inhalation and ingestion. On dermal contact, formaldehyde reacts with proteins of the skin resulting in crosslinking and precipitation of the proteins. Inhalation of formaldehyde vapors produces irritation and inflammation of the bronchi and lungs; once in the lungs, formaldehyde can be absorbed into the blood. Ingestion of formaldehyde is followed immediately by inflammation of the mucosa of the mouth, throat, and gastrointestinal tract (U.S. EPA, 1976). Absorption appears to occur in the intestines (Malorny et al., 1965).

B. Distribution

Following absorption into the blood stream, formaldehyde disappears rapidly due to condensation reactions with tissue components and oxidation to formic acid (U.S. EPA, 1976).

C. Metabolism

The main metabolic pathway for formaldehyde appears to involve initial oxidation to formic acid, followed by further oxidation to CO_2 and H_2O. In rats fed radiolabeled formaldehyde, 40% of the radiolabel was recovered as respiratory CO_2 (Buss et al., 1964). Liver and red blood cells appear to be the major sites for the oxidation of formaldehyde to formic acid (U.S. EPA, 1976; Malorny et al., 1965).

D. Excretion

Some of the formic acid metabolite is excreted in the urine as the sodium salt; most, however, is oxidized to CO_2 and eliminated via the lungs (U.S. EPA, 1976).

IV. HEALTH EFFECTS

A. Carcinogenicity

Watanabe et al. (1954) observed sarcomas at the site of injection in 4 of 10 rats given weekly subcutaneous injections of formaldehyde over 15 months (total dose 260 mg per rat). Tumors of the liver and omentum were reported in two other rats. The authors do not mention any controls.

Groups of mice were exposed to formaldehyde by inhalation at 41 ppm and 81 ppm for one hour a day thrice weekly for 35 weeks. After the initial 35-week exposure to 41 ppm, the mice were

exposed for an additional 29 weeks at 122 ppm. No tumors or metaplasias were found, although numerous changes were observed in respiratory tissues (Horton et al., 1963). The study is considered flawed for several reasons: mice were not observed for a lifetime; survival was poor; many tissues were not examined histologically (U.S. EPA, 1976; U.S. EPA, 1979b).

In a lifetime inhalation study of the combination of hydrochloric acid (10.6 ppm) and formaldehyde (14.6 ppm) vapors in rats, 25/100 animals developed squamous cell carcinomas of the nasal cavity (Nelson, 1979). Nelson also reported that bis-chloromethyl ether, a known carcinogen, was detected in the exposure atmosphere; however, concentrations were not reported.

In a report of interim results (after 16 months of a 2-year study) from a chronic inhalation study of formaldehyde in rats and mice, the Chemical Industry Institute of Toxicology (1979) reported that squamous cell carcinomas of the nasal cavity were observed in three male rats exposed to 15 ppm of formaldehyde (highest dose tested). This type of tumor is extremely rare in unexposed rat of the strain used in this study.

Following receipt of the CIIT (1979) study, the U.S. EPA's Carcinogen Assessment Group (1979c) concluded that "there is substantial evidence that formaldehyde is likely to be a human carcinogen." The unit risk calculation (the lifetime cancer risk associated with continuous exposure to 1 ug/m^3 of formaldehyde) based on the preliminary results from CIIT is estimated to be 3.4 x10^{-5}. This estimate may change when the final results of the CIIT study become available.

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B. Mutagenicity

There is an extensive data base showing that formaldehyde is mutagenic in several species including mice, Drosophila, plants, Saccharomyces cerevisiae, Neurospora Crassa, and several species of bacteria. Formaldehyde also produced unscheduled DNA synthesis in a human cell line. These and other early reports of mutagenic activity have been reviewed by Auerbach et al. (1977) and U.S. EPA (1976).

Reports in the recent literature have supported the finding that formaldehyde is a mutagen: Magana-Schwencke et al. (1978) in a study with S. cerevisiae; Wilkens and MacLeod (1976) in E. coli; Martin et al. (1978) in an unscheduled DNA synthesis test in human HeLa cells; Obe and Beek (1979) in sister chromatid exchange assays in a Chinese hamster ovary (CHO) cell line and in cultured human lymphocytes.

C. Teratogenicity

Formaldehyde has been found negative in teratogenicity assays in beagle dogs (Hurni and Ohden, 1973) and rats (Gofmekler and Bonashevskaya, 1969).

D. Other Reproductive Effects

No changes were observed in the testes of male rats exposed to air concentrations of 1 mg/m^3 of formaldehyde for 10 days (Gofmekler and Bonashevskaya, 1969).

E. Other Chronic Toxicity

Groups of rats, guinea pigs, rabbits, monkeys, and dogs were continuously exposed to approximately 4.6 mg/m^3 of formaldehyde for 90 days. Hematologic values were normal, however, some

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interstitial inflammation occurred in the lungs of all species (Coon et al., 1970).

F. Other Relevant Information

Formaldehyde vapor is quite irritating and is a major cause of the mucous membrane irritation experienced by people exposed to smog. Dermatitis from exposure to formaldehyde is a common problem in workers and consumers who contact the chemical regularly. Formaldehyde is also known to be an allergen in sensitive individuals (U.S. EPA, 1976).

V. AQUATIC EFFECTS

The use of formalin (aqueous formaldehyde) as a chemotherapeutant for control of fungus on fish eggs and ectoparasites on fish is a widely accepted and successful technique. However, unless certain criteria are met formalin may cause acute toxic effects in fish (U.S. EPA, 1976). The acute toxicity of formalin to fish has been reviewed by the U.S. Department of Interior (1973). Analysis of toxicity levels indicates that a wide range of tolerances exist for different species; striped bass appear to be the most sensitive with an LC_{50} of 15 to 35 ppm.

The LC_{50} of formaldehyde for Daphnia magna is reported to range between 100 to 1000 ppm (Dowden and Bennett, 1965). The 48-hour median threshold limit (TLm) for Daphnia was about 2 ppm (McKee and Wolf, 1971).

No effects were observed in crayfish (Procambarus blandingi) exposed to 100 ul/l of formalin (concentration unspecified) for 12 to 72 hours (Helm, 1964).

VI. EXISTING GUIDELINES

The OSHA standard for formaldehyde in workplace air is a time weighted average (TWA) of 3 ppm with a ceiling concentration of 5 ppm (39 CFR 23540). The NIOSH recommended standard is a ceiling concentration of 1.2 mg/m^3 (about 0.8 ppm) (NIOSH, 1976). The ACGIH (1977) recommends a ceiling value of 2 ppm (3 mg/m^3).

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No. 105

Formic Acid

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
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APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

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FORMIC ACID

Summary

There is no information available on the possible carcinogenic, mutagenic, teratogenic, or adverse reproductive effects of formic acid.

Formic acid has been reported to produce albuminuria and hematuria in humans following chronic exposure. Exposure to high levels of the compound may produce circulatory collapse, renal failure, and secondary ischemic lesions in the liver and heart.

Formic acid is toxic to freshwater organisms at concentrations ranging from 120,000 to 2,500,000 ug/l. Daphnia magna was the most sensitive freshwater species tested. Marine crustaceans were adversely affected by exposure to formic acid at concentrations from 80,000 to 90,000 ug/l.

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FORMIC ACID

I. INTRODUCTION

Formic acid (CAS registry number 64-18-6) is a colorless, clear, fuming liquid with a pungent odor (Hawley, 1971; Windholz, 1976; Walker, 1966). It is a naturally formed product, produced by bees, wasps, and ants (Casarett and Doull, 1975). Formic acid has widespread occurrence in a large variety of plants, including pine needles, stinging nettles, and foods (Furia and Bellanca, 1971; Walker, 1966). Industrially, it is made by heating carbon monoxide with sodium hydroxide under heat and pressure, or it may be formed as a coproduct from butane oxidation (Walker, 1966). It has the following physical and chemical constants (Windholz, 1976; Walker, 1966):

Property	Pure	90%	85%
Formula:	CH_2O_2	—	—
Molecular Weight:	46.02	—	—
Melting Point:	8.4°C	-4°C	-12°C
Boiling Point:	100.5°C	—	—
Density:	1.220^{20}_{4}	1.202^{25}_{25}	1.194^{25}_{25}
Vapor Pressure:	33.1 torr @ 20°C		
Solubility:	Miscible in water, alcohol, and ether; soluble in acetone, benzene, and toluene		
Demand (1979):	67.5 million lbs. (CMR, 1979)		

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Formic acid is marketed industrially in 85, 90, and 98 percent aqueous solutions. It is also available at 99+ percent purity on a semicommercial scale. Formic acid is used primarily as a volatile acidulating agent; in textile dyeing and finishing, including carpet printing; in chemical synthesis and pharmaceuticals; and in tanning and leather treatment (CMR, 1979; Walker, 1966).

II. EXPOSURE

A. Water

Formic acid has been detected in raw sewage, in effluents from sewage treatment plants, and in river water (Mueller, et al. 1958). It has also been identified in effluents from chemical plants and paper mills (U.S. EPA, 1976).

B. Food

A large variety of plants contain free formic acid; it has been detected in pine needles, stinging nettle, and fruits (Walker, 1966). It has been identified in a number of essential oils, including petitgrain lemon and bitter orange (Furia and Bellanca, 1971). Formic acid is also reported to be a constitutent of strawberry aroma (Furia and Bellanca, 1971). In the U.S. this chemical may be used as a food additive; allowable limits in food range from 1 ppm in non-alcoholic beverages to 18 ppm in candy (Furia and Bellanca, 1971). It may also occur in food as a result of migration from packaging materials (Sax, 1975).

C. Inhalation

Ambient air concentrations of formic acid range from 4 to 72 ppb (Graedel, 1978). Emission sources include forest fires, plants, tobacco smoke, lacquer manufacture, and combustion of plastics (Graedel, 1978). It

has also been identified in the liquid condensate from the pyrolysis of solid municipal waste (Orphey and Jerman, 1970).

D. Dermal

Pertinent data were not found in the available literature.

III. PHARMACOKINETICS

A. Absorption

Acute toxicity studies in animals and poisoning incidents in man indicate that formic acid is absorbed from the respiratory tract and from the gastrointestinal tract (Patty, 1963; NIOSH, 1977).

B. Distribution

Pertinent data were not found in the available literature.

C. Metabolism

Formate may be oxidized to produce carbon dioxide by the activity of a catalase-peroxide complex, or it may enter the folate-dependent one carbon pool following activation and proceed to carbon dioxide via these reactions (Palese and Tephly, 1975). Species differences in the relative balance of these two pathways for the metabolism of formate have been postulated in order to explain the greater accumulation of formate in the blood of monkeys administered methanol, compared to rats similarly treated (Palese and Tephly, 1975).

D. Excretion

Following intraperitoneal administration of ^{14}C formate to rats, significant amounts of $^{14}CO_2$ were detected in these samples (Palese and Tephly, 1975).

IV. EFFECTS

A. Pertinent data could not be located in the available literature.

B. Chronic Toxicity

Chronic human exposure to formic acid has been reported to produce albuminuria and hematuria (Windholz, 1976).

C. Other Pertinent Information

Formic acid is severely irritating to th skin, eyes, and respiratory tract (NIOSH, 1977). Gleason (1969) has indicated that exposure to high levels of compound may produce circulatory collapse, renal failure, and secondary ischemic lesions in the liver and heart.

V. AQUATIC TOXICITY

A. Acute Toxicity

Dowden and Bennett (1965) demonstrated a 24-hour LC_{50} value of 175,000 µg/l for bluegill sunfish (Lepomis macrochirus) exposed to formic acid. Bringmann and Kuhn (1959) observed a 48-hour LC_{50} value of 120,000 µg/l for waterfleas (Daphnia magna) exposed to formic acid.

Verschueren (1979) reported that a formic acid concentration of 2,500,000 µg/l was lethal to freshwater scuds (Gammarus pulex) and 1,000,000 µg/l was a perturbation threshold value for the fish Trutta iridea.

Portmann and Wilson (1971) determined 48-hour LC_{50} values ranging from 80,000 to 90,000 µg/l for the marine shore crab (Carcinus maenas) exposed to formic acid in static renewal bioassays.

B. Chronic Toxicity

Pertinent data were not found in the available literature.

C. Plant Effects

McKee and Wolf (1963) reported that formic acid at a concentration of 100,000 µg/l was toxic to the freshwater algae, Scenedesmus sp.

D. Residue

Pertinent data were not found in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The eight-hour, TWA exposure limit for occupational exposure to formic acid is 5 ppm (ACGIH, 1977).

B. Aquatic

Hahn and Jensen (1977) have suggested an aquatic toxicity rating range of 100,000 to 1,000,000 µg/l based on 96-hour LC_{50} values for aquatic organisms exposed to formic acid.

FORMIC ACID

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No. 106

Fumaronitrile

Health and Environmental Effects

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DISCLAIMER

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FUMARONITRILE

Summary

Information on the carinogenic, mutagenic, or teratogenic effects of fumaronitrile was not found in the available literature. LD_{50} values for injected mice and orally dosed rats were 38 and 50 mg/kg, respectively. Reports of chronic toxicity studies were not found in the available literature.

FUMARONITRILE

I. INTRODUCTION

This profile is based upon relevant literature identified through mechanized bibliographic searches such as TOXLINE, BIOSIS, Chemical Abstracts, AGRICOLA and MEDLARS, as well as manual searches. Despite approximately 70 citations for fumaronitrile, approximately 95 percent of these concerned the chemistry of fumaronitrile or its reactions with other chemicals. Apparently, the chief use of fumaronitrile is as a chemical intermediate in the manufacture of other chemicals, rather than end uses as fumaronitrile per se. Undoubtedly, this accounts for its low profile in the toxicological literature.

Fumaronitrile or trans-1,2-dicyanoethylene (molecular weight 78.07) is a solid that melts at 96.8°C (Weast, 1975), has a boiling point of 186°C, and a specific gravity of 0.9416 at 25°C. It is soluble in water, alcohol, ether, acetone, chloroform, and benzene. Fumaronitrile is used as a bactericide (Law, 1968), and as an antiseptic for metal cutting fluids (Wantanabe, et al., 1975). It is used to make polymers with styrene numerous other compounds. This compound is easily isomerized to the cis-form, maleonitrile, which is a bactericide and fungicide (Ono, 1979). It is conveniently synthesized from primary amides under mild conditions (Campagna, et al., 1977).

II. EXPOSURE

Human exposure to fumaronitrile from foods cannot be assessed, due to a lack of monitoring data.

Bioaccumulation data on fumaronitrile were not found in the available literature.

III. PHARMACOKINETICS

Specific information on the metabolism, distribution, absorption, or elimination of fumaronitrile was not found in the available literature.

IV. EFFECTS

A. Carcinogenicity, Mutagenicity, Teratogenicity, Reproductive Effects, and Chronic Toxicity

Pertinent data could not be located in the available literature.

B. Acute Toxicity

LD_{50} values for injected mice and orally dosed rats were 38 and 50 mg/kg, respectively (Zeller, et al., 1969).

V. AQUATIC TOXICITY

Data concerning the effects of fumaronitrile to aquatic organisms were not found in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

Data concerning existing guidelines and standards for fumaronitrile were not found in the available literature.

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No. 107

Halomethanes

Health and Environmental Effects

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HALOMETHANES

Summary

The halomethanes are a subcategory of halogenated hydrocarbons. There is little known concerning the chronic toxicity of these compounds. Acute toxicity results in central nervous system depression and liver damage. The fluorohalomethanes are the least toxic. None of the halomethanes have been demonstrated to be carcinogenic; however, chloro-, bromo-, dichloro-, bromodichloro-, and tribromomethane have been shown to be mutagenic in the Ames assay. There are no available data on the teratogenicity of the halomethanes, although both dichloromethane and bromodichloromethane have been shown to affect the fetus.

Brominated methanes appear to be more toxic to aquatic life than chlorinated methanes. Acute toxicity data is rather limited in scope, but reveals toxic concentrations in the range of 11,000 to 550,000 µg/l.

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107-3

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Halomethanes (U.S. EPA, 1979).

The halomethanes are a sub-category of halogenated hydrocarbons. This document summarizes the following halomethanes: chloromethane (methyl chloride); bromomethane (methyl bromide, monobromomethane, embafume); dichloromethane (methylene chloride, methylene dichloride, methylene bichloride); tribromomethane (bromoform); trichlorofluoromethane (trichloromonofluoromethane, fluorotrichloromethane, Frigen 11, Freon 11, Arcton 9); and dichlorodifluoromethane (difluorodichloromethane, Freon 12, Frigen 12, Arcton 6, Genetron 12, Halon, Isotron 2) and bromodichloromethane. These halomethanes are either colorless gases or liquids at environmental temperatures and are soluble in water at concentrations from 13×10^6 to 2.5×10^6 µg/l, except for tribromomethane which is only slightly soluble and bromodichloromethane which is insoluble. Halomethanes are used as fumigants, solvents, refrigerants, and in fire extinguishers. Additional information on the physical/chemical properties of chloromethane, dichloromethane, bromomethane, and bromodichloromethane, can be found in the ECAO/EPA (Dec. 1979) hazard profile on these chemicals.

II. EXPOSURE

A. Water

The U.S. EPA (1975) has identified chloromethane, bromomethane, dichloromethane, tribromomethane, and bromodichloromethane in finished drinking waters in the United States. Halogenated hydrocarbons have been found in finished waters at greater concentrations than in raw waters (Symons, et al. 1975), with the concentrations related to the organic content of the raw water. The concentrations of halomethanes detected in one survey of U.S. drinking waters are:

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Halomethanes in the U.S. EPA Region V
Organics Survey (83 Sites)

Compound	Percent of Locations with Positive Results	Concentrations (mg/l) Median	Maximum
Bromodichloromethane	78	0.006	0.031
Tribromomethane	14	0.001	0.007
Dichloromethane	8	0.001	0.007

Source: U.S. EPA, 1975

Symons, et al. (1975) concluded that trihalomethanes resulting from chlorination are widespread in chlorinated drinking waters. An unexplained increase in the halomethane concentration of water samples occurred in the distribution system water as compared to the treatment plant water.

B. Food

Bromomethane residues from fumigation decrease rapidly from both atmospheric transfer and reaction with proteins to form inorganic bromide residues. With proper aeration and product processing, most residual bromomethane will disappear rapidly due to methylation reactions and volatilization (Natl. Acad. Sci., 1978; Davis, et al. 1977). The U.S. EPA (1979) has estimated the weighted average bioconcentration factors for dichloromethane and tribromomethane to be 1.5 and 14, respectively, for the edible portions of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficient of these two compounds. Bioconcentration factors for the other halomethanes have not been determined.

C. Inhalation

Saltwater atmospheric background concentrations of chloromethane and bromomethane, averaging about 0.0025 mg/m^3 and 0.00036 mg/m^3 respectively, have been reported (Grimsrud and Rasmussen, 1975; Singh, et al. 1977). These values are higher than reported average continental background

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and urban levels suggesting that the oceans may be a major source of global chloromethane and bromomethane. Outdoor bromomethane concentrations as high as 0.00085 mg/m^3 may occur near light traffic. This results from the combustion of ethylene dibromide, a component of leaded gasoline (Natl. Acad. Sci., 1978). Reported background concentrations of dichloromethane in both continental and saltwater atmospheres are about 0.00012 mg/m^3, while urban air concentrations ranged from less than 0.00007 to 0.0005 mg/m^3. Local high indoor concentrations can be caused by the use of aerosol sprays or solvents (Natl. Acad. Sci., 1978). Concentrations of dichlorodifluoromethane and trichlorofluoromethane in the atmosphere over urban areas are several times those over rural or oceanic areas. This probably indicates that the primary modes of entry into the environment, i.e., use of refrigerants and aerosols, are greater in industrialized and populated areas (Howard, et al. 1974). Average concentrations of trichlorofluoromethane reported for urban atmospheres have ranged from nil to 3×10^{-3} mg/m^3, and concentrations for dichlorofluoromethane ranged from 3.5×10^{-3} to 2.9×10^{-2} mg/m^3.

III. PHARMACOKINETICS

A. Absorption

Absorption via inhalation is of primary importance and is fairly efficient for the halomethanes. Absorption can also occur via the skin and gastrointestinal tract, although this is generally more significant for the nonfluorinated halomethanes than for the fluorocarbons (Natl. Acad. Sci., 1978; Davis, et al. 1977; U.S. EPA, 1976; Howard, et al. 1974).

B. Distribution

Halomethanes are distributed rapidly to various tissues after absorption into the blood. Preferential distribution usually occurs to tissues with high lipid content (U.S. EPA, 1979).

C. Metabolism

Chloromethane and bromomethane undergo reactions with sulfhydryl groups in intracellular enzymes and proteins, while bromochloromethane in the body is hydrolyzed in significant amounts to yield inorganic bromide. Dichloromethane is metabolized to carbon monoxide which increases carboxyhemoglobin in the blood and interferes with oxygen transport (Natl. Acad. Sci., 1978). Tribromomethane is apparently metabolized to carbon monoxide by the cytochrome P-450-dependent mixed function oxidase system (Ahmed, et al. 1977). The fluorinated halomethanes form metabolites which bind to cell constituents, particularly when exposures are long-term (Blake and Mergner, 1974). Metabolic data for bromodichloromethane could not be located in the available literature.

D. Excretion

Elimination of the halomethanes and their metabolites occurs mainly through expired breath and urine (U.S. EPA, 1979).

IV. EFFECTS

A. Carcinogenicity

None of the halomethanes summarized in this document are considered to be carcinogenic. Theiss and coworkers (1977) examined the tumorigenic activity of tribromomethane, bromodichloromethane, and dichloromethane in strain A mice. Although increased tumor responses were noted with each, in no case were all the requirements met for a positive carcinogenic response, as defined by Shimkin and Stoner (1975). Several epidemiologic studies have

established an association between trihalomethane levels in municipal drinking water supplies in the United States and certain cancer death rates (various sites) (Natl. Acad. Sci., 1978; Cantor and McCabe, 1977). Cantor, et al. (1978) cautioned that these studies have not been controlled for all confounding variables, and the limited monitoring data that were available may not have been an accurate reflection of past exposures.

B. Mutagenicity

Simmon, et al. (1977) reported that chloromethane, bromomethane, and dichloromethane were all mutagenic to Salmonella typhimurium strain TA100 when assayed in a dessicator whose atmosphere contained the test compound. Metabolic activation was not required. Only marginal positive results were obtained with bromoform and bromodichloromethane. Andrews, et al. (1976) and Jongen, et al. (1978) have confirmed the positive Ames results for chloromethane and dichloromethane, respectively. Dichloromethane was negative in mitotic recombination in S. cerevisiae D3 (Simmon, et al. 1977) and in mutagenicity tests in Drosophila (Filippova, et al. 1967). Trichlorofluoromethane and dichlorofluoromethane were negative in the Ames assay (Uenleke, et al. 1977), and dichlorodifluoromethane in a rat feeding study (Sherman, 1974) caused no increase in mutation rates over controls.

C. Teratogenicity

Pertinent information could not be located in the available literature.

D. Other Reproductive Effects

Gynecologic problems have been reported in female workers exposed to dichloromethane and gasoline vapors (Vozovaya, 1974). Evidence of feto-embryotoxicity has been noted in rats and mice exposed to dichloromethane

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vapor on gestation days 6 to 15 (Schwetz, et al. 1975). Some fetal anomalies were reported in experiments in which mice were exposed to vapor of bromodichloromethane at 8375 mg/m^3, 7 hours/day during gestation days 6 to 15 (Schwetz, et al. 1975).

E. Chronic Toxicity

Schuller, et al. (1978) have observed a suppression of cellular and humoral immune response indices in female ICR mice exposed by gavage for 90 days to bromodichloromethane at 125 mg/kg daily. Tribromomethane suppressed reticuloendothelial system function (liver and spleen phagocytic uptake of Listeria monocytogenes) in mice exposed 90 days at daily doses of 125 mg/kg or less (Munson, et al. 1977,1978). Information pertinent to the chronic toxicity of the other halomethanes could not be located in the available literature.

F. Other Relevant Information

In general, acute intoxication by halomethanes appears to involve the central nervous system and liver function (U.S. EPA, 1979).

V. AQUATIC TOXICITY

A. Acute Toxicity

Acute toxicity studies for halomethanes have obtained acute LC_{50} values for the bluegill sunfish (Lepomis machrochirus) of 11,000 µg/l for methylbromide, 29,300 µg/l for bromoform, 224,000 µg/l for methylene chloride and 550,000 for methyl chloride. A static bioassay produced a 96-hour LC_{50} value of 310,000 µg/l methylene chloride for the fathead minnow (Pimephales promelas) while a flow-through assay produced an LC_{50} value of 193,000 µg/l. In freshwater invertebrates two acute studies with Daphnia

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magna resulted in LC_{50} values of 46,500 µg/l for bromoform, and 224,000 µg/l for methylene chloride. In marine fish, LC_{50} values for the sheepshead minnow (Cyprinodon variegatus) were 17,900 µg/l for bromoform and 180,958 µg/l for methylene chloride. For the tidewater silversides (Menicia beryllina) LC_{50} values of 12,000 µg/l for methylbromide and 147,610 µg/l for methylene chloride were obtained. Adjusted LC_{50} values for the marine mysid shrimp (Mysidopsis bahia) were 24,400 µg/l for bromoform and 256,000 µg/l for methylene chloride (U.S. EPA, 1979).

B. Chronic Toxicity

The only chronic value for an aquatic species was 9,165 µg/l for the sheepshead minnow.

C. Plant Effects

Effective concentrations for chlorophyll a and cell numbers in freshwater algae Selenastrum capricornutum ranged from 112,000 to 116,000 µg/l for bromoform and 662,000 µg/l for methylene chloride, while effective concentrations for the marine algae (Sketonema costatum) were reported as 11,500 to 12,300 µg/l for bromoform and 662,000 µg/l for methylene chloride (U.S. EPA, 1979).

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

Positive associations between human cancer mortality rates and trihalomethanes (chloroform, bromodichloromethane, tribromomethane) in drinking

water have been reported. There have also been positive results for tribromomethane using strain A/St. male mice in the pulmonary adenoma bioassay. Bromomethane, chloromethane, dichloromethane, bromodichloromethane and tribromomethane have been reported as mutagenic in the Ames test without metabolic activation. Dichlorodifluoromethane caused a significant increase in mutant frequency in Neurospora crassa (mold), but was negative in the Ames test. No data implicating trichlorofluoromethane as a possible carcinogen have been published.

Because positive results for the mutagenic endpoint correlate with positive results in in vivo bioassays for oncogenicity, mutagenicity data for the halomethanes suggests that several of the compounds might also be carcinogenic. Since carcinogenicity data currently available for the halomethanes were not adequate for the development of water quality criteria levels, the draft criteria recommended for chloromethane, bromomethane, dichloromethane, tribromomethane and bromodichloromethane are the same as that for chloroform, 2 µg/l.

Chloromethane: OSHA (1976) has established the maximum acceptable time-weighted average air concentration for daily 8-hour occupational exposure at 219 mg/m^3.

Bromomethane: OSHA (1976) has a threshold limit value of 80 mg/m^3 for bromomethane, and the American Conference of Governmental Industrial Hygienists (ACGIH, 1971) has a threshold limit value of 78 mg/m^3.

Dichloromethane: OSHA (1976a,b) has established an 8-hour time-weighted average for dichloromethane of 1,737 mg/m^3, however, NIOSH (1976) has recommended a 10-hour time-weighted average exposure limit of 261 mg/m^3 of dichloromethane in the presence of no more carbon monoxide than 9.9 mg/m^3.

Tribromomethane: OSHA (1976a,b) has established an 8-hour time-weighted average for tribromomethane of 5 mg/m^3.

Bromodichloromethane: There is no currently established occupational exposure standard for bromodichloromethane.

Trichlorofluoromethane and dichlorodifluoromethane: The current OSHA (1976) 8-hour time-weighted average occupational standards for trichlorofluoromethane and dichlorodifluoromethane are 5,600 and 4,950 mg/m^3, respectively. The U.S. EPA (1979) draft water quality criteria for trichlorofluoromethane and dichlorodifluoromethane are 32,000 and 3,000 µg/l, respectively.

B. Aquatic

Draft criteria for the protection of freshwater life have been derived as 24-hour average concentrations for the following halomethanes: methylbromide - 140 µg/l not to exceed 320 µg/l; bromoform - 840 µg/l not to exceed 1,900 µg/l; methylene chloride - 4,000 µg/l not to exceed 9,000 µg/l; and methyl chloride - 7,000 µg/l not to exceed 16,000 µg/l.

Draft criteria for the protection of marine life have been derived as 24- hour average concentrations for the following halomethanes: methylbromide 170 µg/l not to exceed 380 µg/l; bromoform - 180 µg/l not to exceed 420 µg/l; methylene chloride - 1,900 µg/l not to exceed 4,400 µg/l; and methyl chloride - 3,700 µg/l not to exceed 8,400 µg/l.

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HALOMETHANES

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No. 108

Heptachlor

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated heptachlor and has found sufficient evidence to indicate that this compound is carcinogenic.

HEPTACHLOR

Summary

Heptachlor is an organochlorinated cyclodiene insecticide, and has been used mostly in its technical, and hence, impure form, in most bioassays up to the present. Nevertheless, it has been found that heptachlor and its metabolite, heptachlor epoxide, induce liver cancer in mice and rats. Heptachlor was mutagenic in two mammalian assays but not in the Ames test. In long-term reproductive studies in rats, heptachlor caused reduction in litter size, decreased lifespan in suckling rats, and cataracts in both parents and offspring. Little is known about other chronic effects of heptachlor except that it induces alterations in glucose homeostasis. It causes convulsions in humans. Heptachlor epoxide, its major metabolite, accumulates in adipose tissue and is more acutely toxic than the parent compound.

Numerous studies indicate that heptachlor is highly toxic, both acutely and chronically, to aquatic life. Ninety-six hour LC_{50} values for freshwater fish range from 7.0 µg/l to 320 µg/l and 24 to 96-hour LC_{50} values for invertebrates from 0.9 µg/l to 80 µg/l. The 96-hour values for saltwater fish range from 0.8 to 194 µg/l. In a 40-week life cycle test with fathead minnows, the determined no-adverse-effect concentration was 0.86 µg/l. All fish exposed at 1.84 µg/l to heptachlor were dead after 60 days. The fathead minnow bioconcentrated heptachlor and its biodegradation product, heptachlor epoxide, 20,000-fold over ambient water concentrations after 276 days exposure. The saltwater sheepshead minnow accumulated these two compounds 37,000-fold after 126 days exposure. Heptachlor epoxide has approximately the same toxicity values as heptachlor.

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I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Heptachlor (U.S. EPA, 1979).

Heptachlor is a broad spectrum insecticide of the group of polycyclic chlorinated hydrocarbons called cyclodiene insecticides. From 1971 to 1975 the most important use of heptachlor was to control agricultural soil insects (U.S. EPA, 1979).

Pure heptachlor (chemical name 1,4,5,6,7,8,8-heptachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene; $C_{10}H_5Cl_7$; molecular weight 373.35) is a white crystalline solid with a camphor-like odor. It has a vapor pressure of 3×10^{-4} mm Hg at 25°C, a solubility in water of 0.056 mg/l at 25 to 29°C, and is readily soluble in relatively nonpolar solvents (U.S. EPA, 1979).

Technical grade heptachlor (approximately 73 percent heptachlor; 21 percent trans chlordane, 5 percent heptachlor epoxide and 2 percent chlordene isomers) is a tan, soft, waxy solid with a melting range of 46 to 74°C and a vapor pressure of 4×10^{-4} mm Hg at 25°C (U.S. EPA, 1979).

Since 1975, insecticidal uses and production volume have declined extensively because of the sole producer's voluntary restriction and the subsequent issuance of a registration suspension notice by the U.S. EPA, August 2, 1976, for all food crop and home use of heptachlor. However, significant commercial use of heptachlor for termite control and non-food crop pests continues.

Heptachlor persists for prolonged periods in the environment. It is converted to the more toxic metabolite, heptachlor epoxide, in the soil (Lichtenstein, 1960; Lichtenstein, et al. 1970, 1971; Nash and Harris, 1972), in plants (Gannon and Decker, 1958), and in mammals (Davicow and

Radomski, 1953a). Heptachlor, in solution or thin films, undergoes photodecomposition to photoheptachlor (Benson, et al. 1971) which is more toxic than the parent compound to insects (Khan, et al. 1969), aquatic invertebrates (Georgacakis and Khan, 1971; Khan, et al. 1973) and rats, bluegill (Lepomis machrochirus) and goldfish (Carassius auratus) (Podowski, et al. 1979). Photoheptachlor epoxide is also formed in sunlight and is more toxic than the parent compound (Ivie, et al. 1972).

Heptachlor and its epoxide will bioconcentrate in numerous species and will accumulate in the food chain (U.S. EPA, 1979).

II. EXPOSURE

A. Water

Various investigators have detected heptachlor and/or heptachlor epoxide in the major river basins of the U.S. at a mean concentration for both of 0.0063 µg/l (U.S. EPA, 1976). Levels of heptachlor ranged from .001 µg/l to 0.035 µg/l and heptachlor/heptachlor epoxide were found in 25 percent of all river samples (Breidenbach, et al. 1967). Average levels in cotton sediments are around 0.8 µg/kg (U.S. EPA, 1979).

B. Food

In their market basket study (1974-1975) for 20 different cities, the FDA showed that 3 of 12 food classes contained residues of heptachlor epoxide ranging from 0.0006 to 0.003 ppm (Johnson and Manske, 1977). Heptachlor epoxide residues greater than 0.03 mg/kg have been found in 14 to 19 percent of red meat, poultry, and dairy products sampled from 1964-1974 (Nisbet, 1977). Heptachlor and/or heptachlor epoxide were found in 32 percent of 590 fish samples obtained nationally, with whole fish residues from 0.01 to 8.33 mg/kg (Henderson, et al. 1969).

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The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for heptachlor in the edible portions of fish and shellfish consumed by Americans to be 5,200. This estimate is based on measured steady-state bioconcentration factors for sheepshead minnows, fathead minnows, and spot (Leiostomus xanthuru).

Human milk can be contaminated with heptachlor epoxide. A nationwide survey indicated that 63.1 percent of 1,936 mothers' milk samples contained heptachlor epoxide residues ranging from 1 to 2,050 µg/l (fat adjusted) (Savage, 1976). Levels of 5 µg/l of the epoxide have been reported in evaporated milk (Ritcey, et al. 1972).

C. Inhalation

Heptachlor volatilizes from treated surfaces, plants, and soil (Nisbet, 1977). Heptachlor, and to a lesser extent heptachlor epoxide, are widespread in ambient air with typical mean concentratons of approximately 0.5 ng/m^3. On the basis of this data, typical human exposure was calculated to be 0.01 ug/person/day (Nisbet, 1977). Thus, it appears that inhalation is not a major route for human exposure to heptachlor. Air downward from treated fields may contain concentrations as high as 600 ng/m^3. Even after three weeks, the air from these fields may contain up to 15.4 ng/m^3. Thus, sprayers, farmers and nearby residents of sprayed fields may receive significant exposures (Nisbet, 1977).

D. Dermal

Gaines (1960) found rat dermal LD_{50} values of 195 and 250 mg/kg for males and females, respectively, compared with oral LD_{50}'s of 100 and 162 mg/kg, respectively, for technical heptachlor. Thus, dermal exposures may be important in humans under the right exposure conditions.

III. PHARMACOKINETICS

A. Absorption

Heptachlor is readily absorbed from the gastrointestinal tract (Radomski and Davidow, 1953; Mizyukova and Kurchatov, 1970; Matsumura and Nelson, 1971). The degree to which heptachlor is absorbed by inhalation has not been reported (Nisbet, 1977). Percutaneous absorption is less efficient than through the gastrointestinal tract, as indicated by comparison of the acute toxicity resulting from dermal vs. oral exposures (Gaines, 1960).

B. Distribution and Metabolism

Heptachlor reaches all tissues of the rat within one hour of a single oral dose and is metabolized to heptachlor epoxide. Heptachlor has been found to bind to hepatic cytochrome P-450, an enzyme of the liver hydroxylation system (Donovan, et al. 1978). By the end of one month traces of heptachlor epoxide were detectable only in fat and liver. Levels of the epoxide in fatty tissues stabilized 3 to 6 months after a single dose of heptachlor (Mizyukova and Kurchatov, 1970). Human fat samples may also contain nonachlor residues derived from technical heptachlor or chlordane exposure (Sovocool and Lewis, 1975). When experimental animals were fed heptachlor for two months, the highest levels of heptachlor epoxide were found in fat, with lower levels in liver, kidney and muscle and none in brain (Radomski and Davidow, 1953). There is evidence to show that the efficiency of conversion to the epoxide in humans is less than in the rat (Tashiro and Matsumura, 1978). Various researchers have found that heptachlor epoxide is more toxic to mammals than the parent compound (U.S. EPA, 1979). There is an approximate ten to fifteen-fold increase in heptachlor residues found in body fat, milk butterfat, and in the fat of poultry, eggs, and livestock as compared to residue levels found in their normal food rations (U.S. EPA, 1976).

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Heptachlor and its epoxide pass readily through the placenta (U.S. EPA, 1979). The epoxide can be found in over 90 percent of the U.S. population at approximate mean levels of 0.08 to 0.09 mg/kg (Kutz, et al. 1977).

C. Excretion

Elimination of non-stored heptachlor and its metabolites occurs within the first five days, chiefly in the feces and to a lesser extent in the urine (Mizyukova and Kurchatov, 1970). In addition, a primary route for excretion in females is through lactation, mostly as the epoxide. Levels can be as high as 2.05 mg/l (Jonsson, et al. 1977).

IV. EFFECTS

A. Carcinogenicity

The studies on rats have generated much controversy, especially for doses around 10 mg/kg/day. However, heptachlor and/or heptachlor epoxide (1 to 18 mg/kg/day of unspecified purities) have induced hepatocellular carcinomas in mice during three chronic feeding studies. Heptachlor epoxide (also of unspecified purity) has produced the same response in rats in one study (Epstein, 1976; U.S. EPA, 1977). Clearly, studies with chemicals of specified purity still need to be performed to establish if contaminants or species differences are responsible for the observed effects.

B. Mutagenicity

Heptachlor has been reported to be mutagenic in mammalian assays but not in bacterial assays. Heptachlor (1 to 5 mg/kg) caused dominant lethal changes in male rats as demonstrated by the number of resorbed fetuses in intact pregnant rats (Carey, et al. 1973). Bone marrow cells of the treated animals showed increases in the incidence of abnormal mitoses, chromatid abnormalities, pulverization, and translocation. Both heptachlor and heptachlor epoxide induced unscheduled DNA synthesis in SV-40 transformed

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human cells (VA-4) in culture with metabolic activation (Ahmed, et al. 1977). Neither heptachlor nor heptachlor epoxide was mutagenic for Salmonella typhimurium in the Ames test (Marshall, et al. 1976).

C. Teratogenicity

In long-term feeding studies with heptachlor, cataracts developed in the parent rats and in the offspring shortly after their eyes opened (Mestitzova, 1967).

D. Other Reproductive Effects

In long-term feeding studies in rats, heptachlor caused a marked decrease in litter size and a decreased lifespan in suckling rats (Mestitzova, 1967). However, newborn rats were less susceptible to heptachlor than adults (Harbison, 1975).

E. Chronic Toxicity

Little information on chronic effects is available. When administered to rats in small daily doses over a prolonged period of time, heptachlor induced alterations in glucose homeostasis which were thought to be related to an initial stimulation of the cyclic AMP-adenylate cyclase system in liver and kidney cortex (Kacew and Singhal, 1973, 1974; Singhal and Kacew, 1976).

F. Other Relevant Information

Heptachlor is a convulsant (St. Omer, 1971). Rats fed protein-deficient diets are less susceptible to heptachlor and have lower heptachlor epoxidase activities than pair-fed controls (Webb and Miranda, 1973; Miranda, et al. 1973; Miranda and Webb, 1974). Phenobarbital potentiates the toxicity of heptachlor in newborn rats (Harbison, 1975). Many liver and brain enzymes are affected by heptachlor down to 2 mg/kg doses in pigs (U.S. EPA, 1979).

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V. AQUATIC TOXICITY

A. Acute Toxicity

Numerous studies on the acute toxicity of heptachlor to freshwater fish and invertebrate species have been conducted. Many of these studies on heptachlor have used technical grade material. Available data suggest that toxicity of the technical material is attributable to the heptachlor and its degradation product, heptachlor epoxide, and that toxicities of these compounds are similar (Schimmel, et al. 1976). In addition, during toxicity testing with heptachlor, there is apparently an appreciable loss of heptachlor by volatilization due to aeration or mixing, leading to variability of static and flow-through results (Schimmel, et al. 1976; Goodman, et al. 1978).

Fish are less sensitive to heptachlor than are invertebrate species. Ninety-six hour LC_{50} values for fish range from 7.0 µg/l for the rainbow trout, Salmo gairdneri, (Macek, et al. 1969) to 320 µg/l for the goldfish (Carassius auratus). Ten days after a dose of 0.868 µg/g ^{14}C-heptachlor to goldfish, 91.2 percent was unchanged, 5.4 percent was heptachlor epoxide, 1 percent was hydroxychlordene, 1.1 percent was 1-hydroxy-2,3-epoxychlordene and 1.2 percent was a conjugate (Feroz and Khan, 1979). Reported values for invertebrate species range from 0.9 µg/l for the stonefly, Pteronarcella badia, (Sanders and Cope, 1968) to 80 µg/l for the cladoceran (Simocephalus serrulatis). These data indicate that heptachlor is generally highly toxic in acute exposures.

The relative toxicity of heptachlor to its common degradation product, heptachlor epoxide, is 52 µg/l to 120 µg/l as determined in a 26-hour LC_{50} Daphnia magna bioassay (Frear and Boyd, 1967).

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Heptachlor has been shown to be acutely toxic to a number of saltwater fish and invertebrate species. The 96-hour LC_{50} values derived from flow-through tests on four fish species range from 0.85 to 10.5 µg/l (Hansen and Parrish, 1977; Korn and Earnest, 1974; Schimmel, et al. 1976). Results of static exposures of eight fish species are from 0.8 to 194 µg/l (Eisler, 1970; Kutz, 1961). The commercially valuable pink shrimp (Penaeus duorarum) is especially sensitive, with reported 96-hour values as low as 0.03 µg/l (Schimmel, et al. 1976). Other species such as the blue crab, Callinectes sapidus, and American oyster, Crassostrea virginica, are 2,100 and 950 times less sensitive, respectively, than the pink shrimp (Butler, 1963).

B. Chronic Toxicity

In a 40-week life cycle test with fathead minnows (Pimephales promelas), the determined no-adverse-effect concentration was 0.86 µg/l. All fish exposed to 1.84 µg/l were dead after 60 days (Macek, et al. 1976). Valid chronic test data are not available for any aquatic invertebrate species.

In a 28-day exposure starting with sheepshead minnow embryo (Cyprinodon variegatus) growth of fry was significantly reduced at 2.04 µg/l, the safe dose being at 1.22 µg/l (Goodman, et al. 1978). In an 18-week partial life cycle exposure with this same species, egg production was significantly decreased at 0.71 µg/l (Hansen and Parrish, 1977).

C. Plant Effects

In the only study available, a concentration of 1,000 µg/l caused a 94.4 percent decrease in productivity of a natural saltwater phytoplankton community after a 4-hour exposure to heptachlor (Butler, 1963).

D. Residues

The amount of total residues, heptachlor and heptachlor epoxide, accumulated by fathead minnows after 276 days of exposure was found to be

20,000 times the concentration in water (Macek, et al. 1976). Heptachlor epoxide constituted 10-24 percent of the total residue. Adult sheepshead minnows exposed to technical grade material for 126 days accumulated heptachlor and heptachlor epoxide 37,000 times over the concentration of ambient water (Hansen and Parrish, 1977). Juvenile sheepshead minnows exposed in two separate experiments for 28 days bioconcentrated heptachlor 5,700 and 7,518 times the concentration in the water (Hansen and Parrish, 1977; Goodman, et al. 1976).

VI. EXISTING GUIDELINES AND STANDARDS

The issue of the carcinogenicity of heptachlor in humans is being reviewed; thus, it is possible that the human health criterion will be changed.

A. Human

Based on the data for the carcinogenicity of heptachlor epoxide in mice (Davis, 1965), and using the "one-hit" model, the U.S. EPA (1979) has estimated levels of heptachlor/heptachlor epoxide in ambient water which will result in risk levels of human cancer as specified in the table below.

Exposure Assumptions (per day)	Risk Levels and Corresponding Draft Criteria			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish.	0	0.0023 ng/l	0.023 ng/l	0.23 ng/l
Consumption of fish and shellfish only.	0	0.0023 ng/l	0.023 ng/l	0.23 ng/l

Existing Guidelines and Standards

Agency	Published Standard	Reference
Occup. Safety Health Admin.	500 $\mu g/m^3$* on skin from air	Natl. Inst. Occup. Safety Health, 1977
Am. Conf. Gov. Ind. Hyg. (TLV)	500 $\mu g/m^3$ inhaled	Am. Conf. Gov. Ind. Hyg., 1971
World Health Org.	0.5 $\mu g/kg$/day acceptable daily intake in diet	Natl. Acad. Sci., 1977

U.S. Publ. Health Serv. Adv. Comm.	Recommended drinking water standard (1968) 18 µg/l of heptachlor and 18 µg/l of heptachlor epoxide	Natl. Acad. Sci., 1977

*Time weighted average

B. Aquatic

For heptachlor the draft criterion to protect freshwater aquatic life is 0.0015 µg/l as a 24-hour average, not to exceed 0.45 µg/l at any time. To protect saltwater aquatic life, the draft criterion is 0.0036 µg/l as a 24-hour average, not to exceed 0.05 µg/l at any time (U.S. EPA, 1979).

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No. 109

Heptachlor Epoxide

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

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HEPTACHLOR EPOXIDE

SUMMARY

Heptachlor epoxide is the principal metabolite of heptachlor in microorganisms, soil, plants, animals, and probably man, and is more acutely toxic than the parent compound. Its intrinsic effects are difficult to gauge since most of the relevant data in the literature is a side product of the effects of technical heptachlor. Heptachlor epoxide (mostly of unspecified purity) has induced liver cancer in mice and rats and was mutagenic in a mammalian assay system, but not in a bacterial system. Pertinent information on teratogenicity and chronic toxicity could not be located in the available literature. Heptachlor epoxide accumulates in adipose tissue.

The chronic value for the compound derived from a 26-hour exposure of Daphnia magna is reported to be 120 µg/l, approximately the same value obtained for heptachlor.

Fathead minnows bioconcentrated heptachlor and its biodegradation product, heptachlor expoxide, 20,000 times after 276 days of exposure. Heptachlor epoxide constituted between 10 and 24 percent of the total residue.

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HEPTACHLOR EPOXIDE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Heptachlor (U.S. EPA, 1979a).

Heptachlor epoxide is the principal metabolite of heptachlor in microorganisms, soil, plants, and mammals, although the conversion in man may be less efficient (Tashiro and Matsumura, 1978). Since much of the data has been obtained as a side-product of the effects of technical heptachlor and the purity of the epoxide is often unspecified, there is a paucity of reliable literature on its biological effects (U.S. EPA, 1979a).

Heptachlor epoxide is relatively persistent in the environment but has been shown to undergo photodecomposition to photoheptachlor epoxide (Graham, et al. 1973). Photoheptachlor epoxide has been reported to exhibit greater toxicity than heptachlor epoxide (Ivie, et al. 1972). Heptachlor epoxide will bioconcentrate in numerous species and will accumulate in the food chain (U.S. EPA, 1979a).

II. EXPOSURE

A. Water

Heptachlor epoxide has been detected by various investigators in the major river basins of the United States (U.S. EPA, 1979a) at levels ranging from 0.001 to 0.020 µg/l (Breidenbach, et al. 1967).

B. Food

The FDA showed in their market basket survey (1974-1975) of 20 different cities that 3 of 12 food classes con-

tained residues of heptachlor epoxide ranging from 0.0006 to 0.003 ppm (Johnson and Manske, 1977). Heptachlor epoxide residues greater than 0.03 mg/kg were found in 14 to 19 percent of red meat, poultry, and dairy products during the period 1964-1974. Average daily intake was estimated to be between 0.3 to 3 µg from 1965 to 1974 (Nisbet, 1977). Heptachlor and/or heptachlor epoxide were found in 32 percent of 590 fish samples obtained nationally, with whole fish residues containing 0.01 to 8.33 mg/kg (Henderson, et al. 1969). Human milk can be contaminated with heptachlor epoxide; 63 percent of samples in 1975-1976 contained 1 to 2,050 µg/l (fat adjusted) (Savage, 1976). Levels of 5 ng/l have been reported in evaporated milk. Cooking did not reduce the residue level in poultry meat by more than one-half (Ritcey, et al. 1972).

The U.S. EPA (1979a) has estimated the weighted average bioconcentration factor for heptachlor to be 5,200 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on the measured steady-state bioconcentration studies in three species of fish. Since heptachlor epoxide is the primary metabolite of heptachlor and shows greater persistence in body fat (U.S. EPA, 1976), it may be assumed that heptachlor epoxide is bioconcentrated to at least the same extent as heptachlor.

C. Inhalation

Heptachlor epoxide is present in ambient air to a lesser extent than heptachlor and is not thought to con-

tribute substantially to human exposure except in areas near sprayed fields, where concentrations of up to 9.3 $\mu g/m^3$ may be encountered (Nisbet, 1977).

D. Dermal

Gaines (1960) found rat dermal LD_{50} values of 195 and 200 mg/kg for males and females, respectively, compared with oral LD_{50}'s of 100 and 162 mg/kg, respectively, for technical heptachlor. Thus, it is likely that dermal exposure in humans can be important under certain conditions.

III. PHARMACOKINETICS

A. Absorption

Heptachlor epoxide is readily absorbed from the gastrointestinal tract (U.S. EPA, 1979a).

B. Distribution

Studies dealing directly with exposure to heptachlor epoxide could not be located in the available literature. After oral administration of heptachlor to experimental animals, high concentrations of heptachlor epoxide have been found in fat, with much lower levels in liver, kidney, and muscle, and none in brain (Radomski and Davidow, 1953). Another study (Mizyukova and Kurchatav, 1970) also demonstrated the persistence of heptachlor epoxide in fat. Levels in fatty tissues stabilize after three to six months after a single dose. The U.S. EPA (1979a) states that there is approximately 10- to 15-fold increase in heptachlor residues found in body fat, milk butterfat, and in the fat of poultry eggs and livestock as compared to residue levels found in their normal food rations. "Heptachlor residues"

probably refers primarily to heptachlor epoxide. Heptachlor epoxide passes readily through the placenta (U.S. EPA, 1979a) and could be found in over 90 percent of the U.S. population at average levels of around 90 ng/kg (Kutz, et al. 1977).

C. Metabolism and Elimination

Heptachlor epoxide accumulates in adipose tissue, as discussed in the "Distribution" section. The primary route for excretion is fecal (Mizyukova and Kurchatav, 1970). When heptachlor epoxide was fed to rats over a period of 30 days, approximately 20 percent of the administered dose (approximately 5 mg heptachlor epoxide/rat/30 day) was excreted in the feces, primarily as 1-exo-hydroxyheptachlor epoxide and 1,2-dihydroxydihydrochlordene (Matsumura and Nelson, 1971; Tashiro and Matsumura, 1978). In females, a primary route for excretion is via lactation, usually as the epoxide. Levels can be as high as 2.05 mg/l (Jonasson, et al. 1977).

IV. EFFECTS

A. Carcinogenicity

Heptachlor epoxide of unspecified purity induced hepatocellular carcinoma in a chronic feeding study with mice and in one study with rats (Epstein, 1976; U.S. EPA, 1977).

B. Mutagenicity

Heptachlor epoxide induced unscheduled DNA synthesis in SV-40 transformed human cells (VA-4) in culture when metabolically activated (Ahmed, et al. 1977), but was

not mutagenic for Salmonella typhimurium in the Ames test (Marshall, et al. 1976).

C. Teratogenicity, Other Reproductive Effects and Chronic Toxicity

Pertinent data could not be located in the available literature.

D. Other Relevant Information

Heptachlor epoxide is more acutely toxic than heptachlor (U.S. EPA, 1979a). It inhibits synaptic calcium magnesium dependent ATPases in rats (Yamaguchi, et al. 1979).

V. AQUATIC TOXICITY

A. Acute Toxicity

Acute toxicity data could not be located in the available literature relative to the effects of heptachlor epoxide on fish or invertebrates.

B. Chronic Toxicity

In the only reported chronic study, the 26-hour LC_{50} for heptachlor epoxide in Daphnia magna was 120 µg/l (Frear and Boyd, 1967). In the same test, the corresponding value for heptachlor was 52 µg/l.

C. Plant Effects

Data on the toxicity of heptachlor epoxide to plants could not be located in the available literature.

D. Residues

Macek, et al. (1976) determined the bioconcentration factor of 20,000 for heptachlor and heptachlor epoxide in fathead minnows after 276 days' exposure. Heptachlor epoxide residues were reported as constituting 10 to 24 percent of the total residue. The geometric mean bioconcen-

tration factor for heptachlor in all species of fish tested is 11,400 (U.S. EPA, 1979a). As explained in the "Distribution" section of this text, the bioconcentration factor for heptachlor epoxide would be as least as great as that for heptachlor.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The existing guidelines and standards for heptachlor and heptachlor epoxide are:

AGENCY/ORG.	STANDARD	REFERENCE
Occup. Safety Health Admin.	500 $\mu g/m^3$* on skin from air	Natl. Inst. Occup. Safety Health, 1977
Am. Conf. Gov. Ind. Hyg. (TLV)	500 $\mu g/m^3$ inhaled	Am. Conf. Gov. Ind. Hyg., 1971
Fed. Republic Germany	500 $\mu g/m^3$ inhaled	Winell, 1975
Soviet Union	10 $\mu g/m^3$ ceiling value inhaled	Winell, 1975
World Health Organ.**	0.5 µg/kg/day acceptable daily intake in diet	Natl. Acad. Sci., 1977
U.S. Pub. Health Serv. Adv. Comm.	Recommended drinking water standard (1968) 18 µg/l of heptachlor and 18 µg/l heptachlor epoxide	Natl. Acad. Sci., 1977

* Time weighted average

** Maximum residue limits in certain foods can be found in Food Agric. Organ./World Health Organ. 1977, 1978

The U.S. EPA (1979a) is in the process of establishing ambient water quality criteria for heptachlor and heptachlor epoxide. Based on potential carcinogenicity of heptachlor epoxide, the draft criterion is calculated on the esti-

mate that 0.47 ng/man/day would result in an increased additional lifetime cancer risk of no more than 1/100,000. Based on this lifetime carcinogenicity study of heptachlor epoxide at 10 ppm in the diet of C3Heb/Fe/J strain mice, the recommended draft criterion is calculated to be 0.233 ng/l.

B. AQUATIC

No existing guidelines are available for heptachlor epoxide. However, since heptachlor epoxide is a biodegradation product of heptachlor, the hazard profile on heptachlor should be consulted (U.S. EPA, 1979b).

HEPTACHLOR EPOXIDE

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No. 110

Hexachlorobenzene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated hexachlorobenzene and has found sufficient evidence to indicate that this compound is carcinogenic.

HEXACHLOROBENZENE

Summary

Hexachlorobenzene is ubiquitous in the environment and has an extremely slow rate of degradation. Ingested hexachlorobenzene is absorbed readily when associated with lipid material and, once absorbed, is stored for long periods of time in the body fat. Chronic exposures can cause liver and spleen damage and can induce the hepatic microsomal mixed functional oxidase enzyme. Hexachlorobenzene can pass the placental barrier and produce toxic or lethal effects on the fetus. Hexachlorobenzene appears to be neither a teratogen nor a mutagen; however, this compound has produced tumors in both rats and mice.

In the only steady-state study with hexachlorobenzene, the pinfish, Lagodon rhoimboides, bioconcentrated this compound 23,000 times in 42 days of exposure. The concentration of HCB in muscle of pinfish was reduced only 16 percent after 28 days of depuration, a rate similar to that for DDT in fish.

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HEXACHLOROBENZENE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Chlorinated Benzenes (U.S. EPA, 1979).

Hexachlorobenzene (HCB; C_6Cl_6; molecular weight 284.79) is a colorless solid with a pleasant aroma. Hexachlorobenzene has a melting point of 230°C, a boiling point of 322°C, a density of 2.044 g/ml, and is virtually insoluble in water. Hexachlorobenzene is used in the control of fungal diseases in cereal seeds intended solely for planting, as a plasticizer for polyvinyl chloride, and as a flame retardant (U.S. EPA, 1979).

Commercial production of hexachlorobenzene in the U.S. was discontinued in 1976 (Chem. Econ. Hdbk., 1977). However, even prior to 1976, most hexachlorobenzene was produced as a waste by-product during the manufacture of perchloroethylene, carbon tetrachloride, trichloroethylene, and other chlorinated hydrocarbons. This is still the major source of hexachlorobenzene in the U.S., with 2,200 kg being produced by these industries during 1972 (Mumma and Lawless, 1975).

II. EXPOSURE

A. Water

Very little is known regarding potential exposure to hexachlorobenzene as a result of ingestion of contaminated water. Hexachlorobenzene has been detected in specific bodies of water, particularly near points of industrial discharge (U.S. EPA, 1979). Hexachlorobenzene has been detected in the polluted waters of the Mississippi River (usually below 2 ng/kg) and in the clean waters of Lake Superior (concentrations not quantitatively measured). Hexachlorobenzene was detected in drinking water supplies at

three locations, with concentrations ranging from 6 to 10 ng/kg, and in finished drinking water at two locations, with concentrations ranging from 4 to 6 ng/kg (U.S. EPA, 1975).

B. Food

Ingestion of excessive amounts of hexachlorobenzene has been a consequence of carelessness, usually from feeding seed grains to livestock. Foods high in animal fat (e.g., meat, eggs, butter, and milk) have the highest concentrations of hexachlorobenzene. The daily intake of hexachlorobenzene by infants from human breast milk in part of Australia was 39.5 µg per day per 4 kg baby. This exceeded the acceptable daily intake recommended by the FAO/WHO of 2.4 µg/kg/day (1974). The dietary intake by young adults (15 to 18-year old males) was estimated to be 35 µg hexachlorobenzene per person per day (Miller and Fox, 1973). The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for hexachlorobenzene to be 12,000 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficient of hexachlorobenzene.

C. Inhalation

Hexachlorobenzene enters the air by various mechanisms, such as release from stacks and vents of industrial plants, volatilization from waste dumps and impoundments, intentional spraying and dusting, and unintentional dispersion of hexachlorobenzene-laden dust from manufacturing sites (U.S. EPA 1979). No data is given on the concentrations of hexachlorobenzene in ambient air. Significant occupational exposure can occur particularly to pest control operators (Simpson and Chandar, 1972).

D. Dermal

Hexachlorobenzene may enter the body by absorption through the skin as a result of skin contamination (U.S. EPA, 1979).

III. PHARMACOKINETICS

A. Absorption

To date, only absorption of hexachlorobenzene from the gut has been examined in detail. Hexachlorobenzene in aqueous suspensions is absorbed poorly in the intestines of rats (Koss and Koransky, 1975); however, cotton seed oil (Albro and Thomas, 1974) or olive oil (Koss and Koransky, 1975) facilitated the absorption. Between 70 and 80 percent of doses of hexachlorobenzene ranging from 12 mg/kg to 180 mg/kg were absorbed. Hexachlorobenzene in food products will selectively partition into the lipid portion, and hexachlorobenzene in lipids will be absorbed far better than that in an aqueous milieu (U.S. EPA, 1979).

B. Distribution

The highest concentrations of hexachlorobenzene are found in fat tissue (Lu and Metcalf, 1975). In rats receiving a single intraperitoneal (i.p.) injection or oral dose of hexachlorobenzene in olive oil, adipose tissue contained about 120-fold more hexachlorobenzene than muscle tissue; liver, 4-fold; brain, 2.5-fold; and kidney, 1.5-fold (Koss and Koransky, 1975). Adipose tissue serves as a reservoir for hexachlorobenzene, and depletion of fat deposits results in mobilization and redistribution of stored hexachlorobenzene. However, excretion is not increased, and the total body burden is not lowered (Villeneuve, 1975).

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C. Metabolism

Hexachlorobenzene is metabolized after i.p. administration in the rat to pentachlorophenol, tetrachlorohydroquinone and pentachlorothiophenol (Koss, et al. 1976). In another study using rats in which the metabolic products were slightly different, only a small percentage of the metabolites were present as glucuronide conjugates (Engst, et al. 1976). Hexachlorobenzene appears to be an inducer of the hepatic microsomal enzyme system in rats (Carlson, 1978). It has been proposed that both the phenobarbital type and the 3-methylcholanthrene type microsomal enzymes are induced (Stonard, 1975; Stonard and Greig, 1976).

D. Excretion

Hexachlorobenzene is excreted mainly in the feces and, to some extent, in the urine in the form of several metabolites which are more polar than the parent compound (U.S. EPA, 1979). In the rat, 34 percent of the administered hexachlorobenzene was excreted in the feces, mostly as unaltered hexachlorobenzene. Fecal excretion of unaltered hexachlorobenzene is presumed to be due to biliary secretion. Five percent of the administered HCB was excreted in the urine (Koss and Koransky, 1975).

IV. EFFECTS

A. Carcinogenicity

Carcinogenic activity of hexachlorobenzene was assessed in hamsters fed 4.8 or 16 mg/kg/day for life (Cabral, et al. 1977). Whereas 10 percent of the unexposed hamsters developed tumors, 92 percent of the hamsters fed 16 mg/kg/day, 75 percent fed 8 mg/kg/day, and 56 percent fed 4 mg/kg/day developed tumors. The tumors were hepatomas, haemangioendotheliomas and thyroid adenomas. In a study on mice fed 6.5, 13 or 26 mg/kg/day for life, the only increase in tumors was in hepatomas (Cabral, et al. 1978). How-

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ever, the incidence of lung tumors in strain A mice treated three times a week for a total of 24 injections of 40 mg/kg each was not significantly greater than the incidence in control mice (Theiss, et al. 1977). Also, ICR mice fed hexachlorobenzene at 1.5 or 7.0 mg/kg/day for 24 weeks showed no induced hepatocellular carcinomas (Shirai, et al. 1978).

B. Mutagenicity

Hexachlorobenzene was assayed for mutagenic activity in the dominant lethal assay. Rats were administered 60 mg/kg/day hexachlorobenzene orally for ten days; there was no significant difference in the incidence of pregnancies (Khera, 1974).

C. Teratogenicity

Hexachlorobenzene does not appear to be teratogenic for the rat (Khera, 1974). CD-1 mice receiving 100 mg/kg/day hexachlorobenzene orally on gestational days 7 to 11 showed a small increase in the incidence of abnormal fetuses per litter (Courtney, et al. 1976). However, the statistical significance was not mentioned, and the abnormalities appeared in both the exposed and unexposed groups.

D. Other Reproductive Effects

Hexachlorobenzene can pass through the placenta and cause fetal toxicity in rats (Grant, et al. 1977). The distribution of hexachlorobenzene in the fetus appears to be the same as in the adult, with the highest concentration in fatty tissue.

E. Chronic Toxicity

In one long-term study where rats were given 50 mg/kg hexachlorobenzene every other day for 53 weeks, an equilibrium between intake and elimination was achieved after nine weeks. Changes in the histology of the

liver and spleen were noted (Koss, et al. 1978). On human exposure for an undefined time period, porphyrinuria has been shown to occur (Cam and Nigogosyan, 1963).

F. Other Relevant Information

At doses far below those causing mortality, hexachlorobenzene enhances the capability of animals to metabolize foreign organic compounds. This type of interaction may be of importance in determining the effects of other concurrently encountered xenobiotics (U.S. EPA, 1979).

V. AQUATIC TOXICITY

A. No pertinent information is available on acute and chronic toxicity or plant effects.

B. Residues

Hexachlorobenzene (HCB) is bioconcentrated from water into tissues of saltwater fish and invertebrates. Bioconcentration factors (BCF) in short 96-hour exposures are as follow (Parrish, et al. 1974): grass shrimp, Palaeomonetes pugio, - 4,116 µg/l; pink shrimp, Penaeus duorarum, - 1,964 µg/l; sheepshead minnow, Cyprinodon variegatus, - 2,254 µg/l. In a 42-day exposure, the pinfish, Lagodon rhomboides, BCF was 23,000. The concentration of HCB in pinfish muscle was reduced only 16 percent after 28 days of depuration; this slow rate is similar to that for DDT in fish.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

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A. Human

The value of 0.6 µg/kg/day hexachlorobenzene was suggested by FAO/WHO as a reasonable upper limit for residues in food for human consumption (FAO/WHO, 1974). The Louisiana State Department of Agriculture has set the tolerated level of hexachlorobenzene in meat fat at 0.3 mg/kg (U.S. EPA, 1976). The FAO/WHO recommendations for residues in foodstuffs are 0.5 mg/kg in fat for milk and eggs, and 1 mg/kg in fat for meat and poultry (FAO/WHO, 1974). Based on bioassay data, and using the "one-hit" model, the EPA (1979) has estimated levels of hexachlorobenzene in ambient water which will result in specified risk levels of human cancer:

Exposure Assumption (per day)	Risk Levels and Corresponding Draft Criteria			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish.	0	0.0125 ng/l	0.125 ng/l	1.25 ng/l
Consumption of fish and shellfish only.	0	0.0126 ng/l	0.126 ng/l	1.26 ng/l

B. Aquatic

Pertinent information concerning aquatic criteria could not be located in the available literature.

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HEXACHLOROBENZENE

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No. 111

Hexachlorobutadiene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated hexachlorobutadiene and has found sufficient evidence to indicate that this compound is carcinogenic.

HEXACHLOROBUTADIENE

SUMMARY

Hexachlorobutadiene (HCBD) is a significant by-product of the manufacture of chlorinated hydrocarbons. HCBD has been found to induce renal neoplasms in rats (Kociba, et al., 1971). The mutagenicity of HCBD has not been proven conclusively, but a bacterial assay by Taylor (1978) suggests a positive result. Two studies on the possible teratogenic effects of HCBD produced conflicting results.

Ninety-six hour LC_{50} values for the goldfish, snail, and sowbug varied between 90 and 210 µg/l in static renewal tests. Measured bioconcentration factors after varying periods of exposure are as follows: crayfish, 60; goldfish, 920-2,300; Scuyemouth bass, 29; and an alga, 160.

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HEXACHLOROBUTADIENE

I. INTRODUCTION

Hexachlorobutadiene (HCBD) is produced in the United States as a significant by-product in the manufacture of chlorinated hydrocarbons such as tetrachloroethylene, trichloroethylene, and carbon tetrachloride. This secondary production in the U.S. ranges from 7.3 to 14.5 million pounds per year, with an additional 0.5 million pounds being imported (U.S. EPA, 1975).

HCBD is used as an organic solvent, the major domestic users being chlorine producers. Other applications include its use as an intermediate in the production of rubber compounds and lubricants. HCBD is a colorless liquid with a faint turpentine-like odor. Its physical properties include: boiling point, 210-220°C vapor pressure, 0.15 mm Hg; and water solubility of 5 µg/l at 20°C (U.S. EPA, 1979).

Environmental contamination by HCBD results primarily during the disposal of wastes containing HCBD from chlorinated hydrocarbon industries (U.S. EPA, 1976). It has been detected in a limited number of water samples. HBCD appears to be rapidly adsorbed to soil and sediment from contaminated water, and concentrates in sediment from water by a factor of 100 (Leeuwangh, et al., 1975).

II. EXPOSURE

A. Water

HCBD contamination of U.S. finished drinking water supplies does not appear to be widespread. The problem is localized in areas with raw water sources near industrial

plants discharging HBCD. From its physical and chemical properties, HBCD removal from water by adsorption into sediment should be rapid (Laseter, et al., 1976). Effluents from various industrial plants were found to contain HCBD levels ranging from 0.04 to 240 µg/l (Li, et al., 1976). An EPA study of the drinking water supply of ten U.S. cities revealed that HCBD was detected in one of the water supplies, but the concentration was less than 0.01 µg/l (U.S. EPA, 1975).

B. Food

Since the air, soil and water surrounding certain chlorohydrocarbon plants have been shown to be contaminated with HCBD (Li, et al., 1976), food produced in the vicinity of these plants might contain residual levels of HCBD. A survey of foodstuffs produced within 25 miles of tetrachloroethylene and trichloroethylene plants did not detect measurable levels of HCBD. Freshwater fish caught in the lower Mississippi contained HBCD residues in a range from 0.01 to 1.2 mg/kg. Studies on HCBD contamination of food in several European countries have measured levels as high as 42 µg/kg in certain foodstuffs (Kotzias, et al., 1975).

The U.S. EPA (1979) has estimated a HCBD bioconcentration factor of 870 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on measured steady-state bioconcentration studies in goldfish.

C. Inhalation

The levels of HCBD detected in the air surrounding chlorohydrocarbon plants are generally less than 5 $\mu g/m^3$,

although values as high as 460 $\mu g/m^3$ have been measured (Li, et al. 1976).

III. PHARMACOKINETICS

A. Absorption

Pertinent data were not found on the absorption of HCBD in the available literature.

B. Distribution

HCBD did not have a strong tendency to accumulate in fatty tissue when administered orally with other chlorinated hydrocarbons. Some of the chlorinated hydrocarbons were aromatic compounds and accumulated significantly in fat (Jacobs, et al. 1974).

C. Metabolism

Pertinent data were not found in the available literature.

D. Excretion

Pertinent data were not found in the available literature.

IV. EFFECTS ON MAMMALS

A. Carcinogenicity

Kociba, et al. (1977) administered dietary levels of HCBD ranging from 0.2 mg/kg/day to 20.0 mg/kg/day for two years to rats. In males receiving 20 mg/kg/day, 18 percent (7/39) had renal tubular neoplasms which were classified as adenocarcinomas; 7.5 percent (3/40) of the females on the high dose developed renal carcinomas. Metastasis to the lung was observed in one case each for both male and female rats.

No carcinomas were observed in controls, however, a nephroblastoma developed in one male and one female.

A significant increase in the frequency of lung tumors was observed in mice receiving intraperitoneal injections of 4 mg/kg or 8 mg/kg of HCBD, three times per week until totals of 52 mg and 96 mg, respectively, were administered (Theiss, et al. 1977).

B. Mutagenicity

Taylor (1978) tested the mutagenicity of HCBD on S. typhimurium TA100. A dose dependent increase in reversion rate was noted, but the usual criterion for mutagenicity of double the background rate was not reached.

C. Teratogenicity

Poteryaeva (1966) administered HCBD to nonpregnant rats by a single subcutaneous injection of 20 mg/kg. After mating, the pregnancy rate for the dosed rats was the same as that of controls. The weights of the young rats from the dosed mothers were markedly lower than the controls. Autopsies at 2-1/2 months revealed gross pathological changes in internal organs including glomerulonephritis of the kidneys. Degenerative changes were also observed in the red blood cells.

D. Other Reproductive Effects

Schwetz, et al. (1977) studied the effects of dietary doses of HCBD on reproduction in rats. Males and females were fed dose levels of 0.2 to 20 mg/kg/day HCBD starting 90 days prior to mating and continuing through lactation. At the two highest doses, adult rats suffered weight loss,

decreased food consumption and alterations of the kidney cortex, while the only effect on weanlings consisted of a slight increase in body weight at 21 days of age at the 20 mg/kg dose level. Effect on survival of the young was not effected.

E. Chronic Toxicity

The kidney appears to be the organ most sensitive to HCBD. Possible chronic effects are observed at doses as low as 2 to 3 mg/kg/day (Kociba, et al., 1971, 1977; Schwetz, et al., 1977). Single oral doses as low as 8.4 mg/kg have been observed to have deleterious effects on the kidney (Schroit, et al. 1972). Neurotoxic effects in rats have been reported at a dose of 7 mg/kg and effects may occur at even lower dose levels (Poteryaeva, 1973; Murzakaev, 1967). HCBD at 0.004 mg/kg gave no indication of neurotoxicity. Acute HCBD intoxication affects acid-base equilibrium in blood and urine (Popovich, 1975; Poteryaeva, 1971). Some investigators report a cumulative effect for HCBD during chronic dosing by dermal (Chernokan, 1970) or oral Poteryaeva, 1973) routes. An increase in urinary coproporphyrin was observed in rats receiving 2 mg/kg/day and 20 mk/kg/day HCBD for up to 24 months (Kociba, 1977).

F. Other Relevant Information

The possible antagonistic effect of compounds containing mercapto (-SH) groups on HCBD have been suggested by two studies. Murzokaev (1967) demonstrated a reduction in free -SH groups in cerebral cortex homogenate and blood serum following HCBD injection in rats. Mizyukova, et al. (1973) found thiols (-SH compounds) and amines to be effective anti-

dotes against the toxic effects of HCBD when administered prior to or after HCBD exposure.

V. AQUATIC TOXICITY

A. Acute Toxicity

Goldfish, (Carassius auratus), had an observed 96-hour LC_{50} of 90 µg/l in a static renewal test (Leeuwangh, et al. 1975). A snail, (Lymnaea stagnalis), and a sowbug, (Asellus aquaicus), were both exposed for 96-hours to HCBD resulting in EC_{50} values of 210 and 130 µg/l, respectively (Leeuwangh, et al., 1975). No acute studies with marine species have been conducted.

B. Chronic Toxicity

Pertinent information was not found in the available literature.

C. Plant Effects

Pertinent data was not found in the available literature.

D. Residues

Measured bioconcentration factors are as follows: crayfish, Procambaeus clarhi, 60 times after 10 days exposure; goldfish, Caressius auretus, 920-2,300 times after 49 days exposure; large mouth bass, Microptorus salmoides, 29 times after 10 days exposure; and a freshwater alga, Oedogonium cardiacum, 160 times after 7 days exposure (Laseter, et al., 1976). Residue data on saltwater organisms are not available.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria may be changed.

A. Human

Standards or guidelines for exposure to HCBD are not available.

The draft ambient water quality criteria for HCBD have been calculated to reduce the human carcinogenic risk levels to 10^{-5}, 10^{-6}, and 10^{-7} (U.S. EPA, 1979). The corresponding criteria are 0.77 µg/l, 0.077 µg/l, 0.0077 µg/l, respectively.

B. Aquatic

Draft freshwater or saltwater criterion for hexachlorobutadiene have not been developed because of insufficient data (U.S. EPA, 1979).

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No. 112

Hexachlorocyclohexane

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated hexachlorocyclohexane and has found sufficient evidence to indicate that this compound is carcinogenic.

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HEXACHLOROCYCLOHEXANE

Summary

Hexachlorocyclohexane (HCH), a broad spectrum insecticide, is a mixture of five configurational isomers. HCH is no longer used in the United States; however, its gamma-isomer, commonly known as lindane, continues to have significant commercial use. Technical HCH, alpha-HCH, beta-HCH, and lindane (gamma-HCH) have all been shown to induce liver tumors in mice. Most of the studies on hexachlorocyclohexanes deal only with lindane. Evidence for mutagenicity of lindane is equivocal. Lindane was not teratogenic for rats, although it reduced reproductive capacity in rats in a study of four generations. Chronic exposure of animals to lindane caused liver enlargement and, at higher doses, some liver damage and nephritic changes. Humans chronically exposed to HCH suffered liver damage. Chronic exposure of humans to lindane produced irritation of the central nervous system. HCH and lindane are convulsants. The U.S. EPA (1979) has estimated the ambient water concentrations of hexachlorocyclohexanes corresponding to a lifetime cancer risk for humans of 10^{-5} as follows: 21 ng/l for technical HCH, 16 ng/l for alpha-HCH, 28 ng/l for beta-HCH, and 54 ng/l for lindane (gammaHCH).

Lindane has been studied in a fairly extensive series of acute studies for both freshwater and marine organisms. Acute toxic levels as low as 0.17 ng/l have been reported for marine invertebrate species.

HEXACHLOROCYCLOHEXANE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Hexachlorocyclohexane (U.S. EPA, 1979). 1,2,3,4,5,6-Hexachlorocyclohexane ($C_6H_6Cl_6$; molecular weight 290.0) is a brownish-to-white crystalline solid with a melting point of 65°C and a solubility in water of 10 to 32 mg/l. It is a mixture of five configurational isomers and is commonly referred to as BHC or benzene hexachloride. Lindane is the common name for the gamma isomer of 1,2,3,4,5,6-hexachlorocyclohexane (U.S. EPA, 1979).

Technical grade hexachlorobenzene (HCH) contains the hexachlorocyclohexane isomers in the following ranges: alpha-isomer, 55 to 70 percent; beta-isomer, 6 to 8 percent; gamma-isomer, 10 to 18 percent; delta-isomer, 3 to 4 percent; epsilon-isomer, trace amounts. Technical grade HCH may also contain 3 to 5 percent of other chlorinated derivatives of cyclohexane, primarily heptachlorocyclohexane and octachlorocyclohexane (U.S. EPA, 1979).

Hexachlorocyclohexane (HCH) is a broad spectrum insecticide of the group of cyclic chlorinated hydrocarbons called organochlorine insecticides. Since the gamma-isomer (lindane) has been shown to be the insecticidally active ingredient in technical grade HCH, technical grade HCH has had limited commercial use except as the raw material for production of lindane. Use of technical HCH has been banned in the U.S., but significant commercial use of lindane continues. Lindane is used in a wide range of applications including treatment of animals, buildings, man (for ectoparasites), clothes, water (for mosquitoes), plants, seeds, and soils (U.S. EPA, 1979).

No technical grade HCH or lindane is currently manufactured in the U.S.; all lindane used in the U.S. is imported (U.S. EPA, 1979).

Lindane has a low residence time in the aquatic environment. It is removed by sedimentation, metabolism, and volatilization. Lindane contributes less to aquatic pollution than the other hexachlorocyclohexane isomers (Henderson, et al. 1971).

Lindane is slowly degraded by soil microorganisms (Mathur and Saha, 1975; Tu, 1975, 1976) and is reported to be isomerized to the alpha and/or delta isomers in microorganisms and plants (U.S. EPA, 1979), though this is controversial (Tu, 1975, 1976; Copeland and Chadwick, 1979; Engst, et al. 1977). It is not isomerized in adipose tissues of rats, however (Copeland and Chadwick, 1979).

II. EXPOSURE

A. Water

The contamination of water has occurred principally from direct application of technical hexachlorocyclohexane (HCH) or lindane to water for control of mosquitoes, from the use of HCH in agriculture and forestry, and, to a lesser extent, from occasional contamination of wastewater from manufacturing plants (U.S. EPA, 1979).

In the finished water of Streator, Illinois, lindane has been detected at a concentration of 4 µg/l (U.S. EPA, 1975).

B. Food

The daily intake of lindane has been reported to be 1 to 5 µg/kg body weight and the daily intake of all other HCH isomers to be 1 to 3 µg/kg body weight (Duggan and Duggan, 1973). The chief sources of HCH residues in the human diet are milk, eggs, and other dairy products (U.S. EPA, 1979), and carrots and potatoes (Lichtenstein, 1959). Seafood is usually a minor

source of HCH, probably because of the relatively high rate of dissipation of HCH in the aquatic environment (U.S. EPA, 1979).

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for lindane to be 780 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on measured steady-state bioconcentration in bluegills.

C. Inhalation

Traces of HCH have been detected in the air of central and suburban London (U.S. EPA, 1979). No further pertinent information could be found in the available literature.

D. Dermal

Lindane has been used to eradicate human ectoparasites and few adverse reactions have been reported (U.S. EPA, 1979).

III. PHARMACOKINETICS

A. Absorption

The rapidity of lindane absorption is enhanced by lipid mediated carriers. Compared to other organochlorine insecticides, HCH and lindane are unusually soluble in water, which contributes to rapid absorption and excretion (Herbst and Bodenstein, 1972; U.S. EPA, 1979). Intraperitoneal injection of lindane resulted in 35 percent absorption (Koransky, et al. 1963). Lindane is absorbed after oral and dermal exposure (U.S. EPA, 1979).

B. Distribution

After administration to experimental animals, lindane was detected in the brain at higher concentrations than in other organs (Laug, 1948; Davidow and Frawley, 1951; Koransky, et al. 1963; Huntingdon Res. Center,

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1972). At least 75 percent of an intraperitonial dose of ^{14}C-labeled lindane was consistently found in the skin, muscle, and fatty tissue (Koransky, et al. 1963). Lindane enters the human fetus through the placenta; higher concentrations were found in the skin than in the brain and never exceeded the corresponding values for adult organs (Poradovsky, et al. 1977; Nishimura, et al. 1977).

C. Metabolism

Lindane is metabolized to gamma-3,4,5,6-tetrachlorocyclohexene in rat adipose tissue, but is not isomerized (Copeland and Chadwick, 1979); other metabolites are 2,3,4,5,6-pentachloro-2-cyclohexene-1-ol, two tetrachlorophenols, and three trichlorophenols (Chadwick, et al. 1975; Engst, et al. 1977). These are commonly found in the urine as conjugates (Chadwick and Freal, 1972). Lindane metabolic pathways are still matters of some controversy (Engst, et al. 1977; Copeland and Chadwick, 1979). Hexachlorocyclohexane isomers other than lindane are metabolized to trichlorophenols and mercapturic acid conjugates (Kurihara, 1979). Both free and conjugated chlorophenols are far less toxic than the parent compounds (Natl. Acad. Sci., 1977).

D. Excretion

HCH and lindane appear to be eliminated primarily as conjugates in the urine. Elimination of lindane appears to be rapid after administration ceases. Elimination of beta-HCH is much slower (U.S. EPA, 1979). In females, HCH is excreted in the milk as well as in the urine. The beta-isomer usually accounts for above 90 percent of the HCH present in human milk (Herbst and Bodenstein, 1972).

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IV. EFFECTS

A. Carcinogenicity

An increased incidence of liver tumors was reported in male and/or female mice of various strains fed technical hexachlorocyclohexane (Goto, et al. 1972; Hanada, et al. 1973; Nagasaki, et al. 1972), alpha-HCH (Goto, et al. 1972; Hanada, et al. 1973; Ito, et al. 1973, 1975), beta-HCH (Goto, et al. 1972; Thorpe and Walker, 1973) and lindane (gamma-HCH) (Goto, et al. 1972; Hanada, et al. 1973; Natl. Cancer Inst., 1977a; Thorpe and Walker, 1973). Male rats fed alpha-HCH also developed liver tumors (Ito, et al. 1975). A mixture containing 68.7 percent alpha-HCH, 6.5 percent beta-HCH and 13.5 percent lindane in addition to other impurities (hepta- and octa-chlorocyclohexanes), administered orally (100 ppm in the diet, or 10 mg/kg body weight by intubation), caused tumors in liver and in lymph-reticular tissues in male and female mice after 45 weeks. Application by skin painting had no effect (Kashyap, et al. 1979). A review by Reuber (1979) suggests that lindane is carcinogenic on uncertain evidence.

B. Mutagenicity

Evidence for the mutagenicity of lindane is equivocal. Some alterations in mitotic activity and the karyotype of human lymphocytes cultured with lindane at 0.1 to 10 µg/ml have been reported (Tsoneva-Maneva, et al. 1971). Lindane was not mutagenic in a dominant-lethal assay (U.S. EPA, 1973) or a host-mediated assay (Buselmair, et al. 1973).

Gamma-HCH was found to be mutagenic in microbial assays using Salmonella typhimurium with metabolic activation, the host-mediated assay, and the dominant lethal test in rats. Other reports indicate that it does not have significant mutagenic activity (U.S. EPA, 1979).

C. Teratogenicity

Lindane given in the diet during pregnancy at levels of 12 or 25 mg/kg body weight/day did not produce teratogenic effects in rats (Mametkuliev, 1978; Khera, et al. 1979).

D. Other Reproductive Effects

Chronic lindane feeding in a study of four generations of rats increased the average duration of pregnancy, decreased the number of births, increased the proportion of stillbirths, and delayed sexual maturation in F_2 and F_3 females. In addition, some of the F_1 and F_2 animals exhibited spastic paraplegia (Petrescu, et al. 1974).

In rats and rabbits, lindane given in the diet during pregnancy increased postimplanation death of embryos (Mametkuliev, 1978; Palmer, et al. 1978). Testicular atrophy has been observed for lindane in rats and mice (National Cancer Institute, 1977b; Nigam, et al. 1979).

E. Chronic Toxicity

Irritation of the central nervous system, with other toxic side effects (nausea, vomiting, spasms, weak respiration with cyanosis and blood dyscrasia), was reported after prolonged or improper use of Hexicid (1 percent lindane) for the treatment of scabies on humans (Lee, et al. 1976). Production workers exposed to technical HCH exhibited symptoms including headache, vertigo, irritation of the skin, eyes, and respiratory tract mucosa. In some instances, there were apparent disturbances of carbohydrate and lipid metabolism and dysfunction of the hypothalamo-pituitary-adrenal system (Kazahevich, 1974; Besuglyi, et al. 1973). A study of persons occupationally exposed to HCH for 11 to 23 years revealed biochemical manifestations of toxic hepatitis (Sasinovich, et al. 1974).

In chronic studies with rats given lindane in oil, liver cell hypertrophy (fat degeneration and necrosis) and nephritic changes were noted at higher doses (Fitzhugh, et al. 1950; Lehman, 1952). Rats inhaling lindane (0.78 mg/m^3) for seven hours, five days a week for 180 days showed liver cell enlargement, but showed no toxic symptoms or other abnormalities (Heyroth, 1952). The addition of 10 ppm lindane to the diet of rats for one or two years decreased body weight after five months of treatment and altered ascorbic acid levels in urine, blood, and tissues (Petrescu, et al. 1974). Dogs chronically exposed to lindane in the diet had slightly enlarged livers (Rivett, et al. 1978).

F. Other Relevant Information

Hexachlorocyclohexane is a convulsant.

Lindane is the most acutely toxic isomer of HCH. The toxic effects of lindane are antagonized by pretreatment with phenobarbital (Litterst and Miller, 1975) and by treatment with silymarin (Szpunar, et al. 1976) and various tranquilizers (Ulmann, 1972).

V. AQUATIC TOXICITY

A. Acute Toxicity

Among 16 species of freshwater fish, LC_{50} values from one flow-through and 24 static bioassays for the gamma isomer of hexachlorocyclohexane ranged from 2 µg/l for the brown trout (Salmo trutta) (Macek and McAllister, 1970) to 152 µg/l for the goldfish (Carassius auratus) (Henderson, et al. 1959). In general, the salmon tended to be more sensitive to the action of lindane than did warm water species. Zebrafish (Brachydanio rerio) showed a lindane LC_{50} value of 120 ng/l, but rainbow trout (Salmo gairdneri) evidenced respiratory distress at 40 ng/l (Slooff, 1979). Technical grade HCH was much less toxic than pure lindane; LC_{50}

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values obtained for lindane in 96-hour studies of the freshwater goldfish (Carassius auratus) ranged from 152 µg/l for 100 percent lindane to 8,200 µg/l for BCH (15.5 percent gamma isomer) (Henderson, et al. 1959). Static tests on freshwater invertebrates revealed a range of LC_{50} values of from 4.5 µg/l (96-hour test) (Sanders and Cope, 1968) for the stonefly (Pteronarcys californica) to 880 µg/l (48-hour test) (Sanders and Cope, 1968) for the clado- ceran (Simocephalus serralatus) for lindane. Canton and Slooff (1977) re- ported an LC_{50} value for the pond snail (Lymnaea stagnalis) of 1,200 µg/l for alpha-HCH in a 48-hour static test.

Among seven species of marine fish tested for the acute effects of lindane, static test LC_{50} values ranged from 9.0 µg/l for the Atlantic silversides (Menidia menidia) to 66.0 µg/l for the striped mullet (Mugil cephalus) (Eisler, 1970). The results of six flow-through assays on five species of marine fish produced LC_{50} values from 7.3 µg/l for the striped bass (Morone saxatilis) (Korn and Earnest, 1974) to 240 µg/l for the long nose killifish (Fundulus similis) (Butler, 1963). A single species, the pinfish (Lagodon rhomboides), tested with technical grade hexachlorocyclo- hexane, produced a 96-hour flow-through LC_{50} value of 86.4 µg/l (Schimmel, et al. 1977). Acute tests on marine invertebrates showed six species to be quite sensitive to lindane, with LC_{50} values from both static and flow- through assays ranging from 0.17 µg/l for the pink shrimp (Panaeus duorarum) (Schimmel, et al. 1977) to 10.0 µg/l for the grass shrimp (Palaemonetas vulgaris) (U.S. EPA, 1979) An LC_{50} value of 0.34 µg/l was obtained for technical grade hexachlorocyclohexane for the pink shrimp (Schimmel, et al. 1977). The American oyster had an EC_{50} of 450 µg/l based on shell decom- position (Butler, 1963).

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B. Chronic

A chronic value of 14.6 µg/l for lindane was obtained in a life-cycle assay of the freshwater fathead minnow (Pimephales promelas). For three species of freshwater invertebrates tested with lindane, chronic values of 3.3, 6.1, and 14.5 µg/l were obtained for Chironomus tentans, Gammarus fasciatus, and Daphnia magna (Macek, et al. 1976). No chronic marine data for any of the hexachlorobenzenes were available.

C. Plant Effects

Concentrations causing growth inhibition of the freshwater alga, Scenedesmus acutus were reported to be 500, 1,000, 1,000, and 5,000 µg/l for alpha-HCH, technical grade HCH, lindane, and beta-HCH, respectively (Krishnakumari, 1977). In marine phytoplankton communities, an effective concentration value of 1,000 µg/l (resulting in decreased productivity) was reported for lindane; and for the alga, Acetabularia mediterranea an effective concentration of 10,000 µg/l was obtained for lindane-induced growth inhibition. No effect in 48 hours was observed for the algae Chlamydomonas sp. exposed to lindane at the maximum solubility limit. Irreparable damage to Chlorella sp. occurred at lindane concentrations of more than 300 µg/l (Hansen, 1979).

D. Residues

Bioconcentration factors for lindane ranging from 35 to 938 were reported for six species of freshwater organisms (U.S. EPA, 1979; Sugiura, et al. 1979a). In marine organisms, bioconcentration factors (after 28 days) for 39 percent lindane of 130, 218, and 617 were obtained for the edible portion of the pinfish (Lagodon rhomboides), the American oyster

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(Crassostrea virginica), and offal tissue of the pinfish (Schimmel, et al. 1977). Sugiura, et al. (1979a) found alpha-, beta-, and gamma-HCH had accumulation factors of 1,216, 973 and 765 in golden orfe (Leuciscusidus melanotus); 330, 273, and 281 in carp (Cyprinus carpio); 605, 658, and 442 in brown trout (Salmo trutta fario); and 588, 1,485, and 938 in guppy (Poecila reticula), respectively. Further, these accumulation factors were proportional to the lipid content of the fish. Accumulation occurred in the adipose tissues and the gall bladder, with the alpha and beta-HCH being more persistent (Sugiura, et al. 1979b).

Equilibrium accumulation factors of 429 to 602 were observed at days 2 to 6 after exposure of Chlorella sp. to 10 to 400 µg/l of lindane in aqueous solution (Hansen, 1979).

VI. EXISTING STANDARDS AND GUIDELINES

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

Based on the induction of liver tumors in male mice, and using the "one-hit" model, the U.S. EPA (1979) has estimated the following levels of technical hexachlorocyclohexane and its isomers in ambient water which will result in specified risk levels of human cancer.

The water concentrations of technical HCH corresponding to a lifetime cancer risk for humans of 10^{-5} is 21 ng/l, based on the data of Nagasaki, et al. (1972).

The water concentrations of alpha-HCH corresponding to a lifetime cancer risk for humans of 10^{-5} is 16 ng/l, based on the data of Ito, et al. (1975).

The water concentrations of beta-HCH corresponding to a lifetime cancer risk for humans of 10^{-5} is 28 ng/l, based on the data of Goto, et al. (1972).

The water concentrations of lindane (gamma-HCH) corresponding to a lifetime cancer risk for humans of 10^{-5} is 54 ng/l, based on the data of Thorpe and Walker (1973).

Data for the delta and epsilon isomers are insufficient for the estimation of cancer risk levels (U.S. EPA, 1979).

An ADI of 1 µg/kg for HCH has been set by the Food and Agricultural Organization and the World Health Organization (U.S. EPA, 1979).

Tolerance levels set by the EPA are as follows: 7 ppm for animal fat, 0.3 ppm for milk, 1 ppm for most fruits and vegetables, 0.004 pm for finished drinking water, and 0.5 $\mu g/m^3$ (skin) for air (U.S. EPA, 1979).

B. Aquatic

For lindane, freshwater criteria have been drafted as 0.21 µg/l with 24-hour average concentration not to exceed 2.9 µg/l. For marine organisms, criteria for lindane have not been drafted. No criteria for mixtures of isomers of hexachlorocyclohexane (benzene hexachloride) were drafted for freshwater or marine organisms because of the lack of data.

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No. 113

gamma-Hexachlorocyclohexane

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

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Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

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GAMMA-HEXACHLOROCYCLOHEXANE (Lindane)

Summary

Gamma-1,2,3,4,5,6-hexachlorocyclohexane, commonly known as lindane, can induce liver tumors in mice. Evidence for mutagenicity of lindane is equivocal. Lindane was not teratogenic for rats, although it reduced reproductive capacity over four generations. Chronic exposure of animals to lindane caused liver enlargement and, at higher doses, some liver damage and nephritic changes. Humans chronically exposed to HCH suffered liver damage. Chronic exposure of humans to lindane produced irritation of the central nervous system. Lindane is a convulsant.

Lindane has been extensively studied in a number of freshwater and marine acute studies. Levels as low as 0.17 µg/l are toxic to marine invertebrate species.

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GAMMA-HEXACHLOROCYCLOHEXANE (Lindane)

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Hexachlorocyclohexane (U.S. EPA, 1979).

Gamma-1,2,3,4,5,6-hexachlorocyclohexane or lindane ($C_6H_6Cl_6$; molecular weight 290.0) is a crystalline solid with a melting point of 112.8°C, a vapor pressure of 0.003 mm Hg at 20°C (U.S. EPA, 1979), a solubility in water at 25°C of 7.8 mg/l (Hansen, 1979), and a solubility in ether of 20.8 g/100 g at 20°C (U.S. EPA, 1979). Other trade names include Jacutin, Lindfor 90, Lindamul 20, Nexit-Staub, Prodactin, gamma-HCH, gamma-BHC, and purified BHC (U.S. EPA, 1979). Technical grade hexachlorocyclohexane contains 10 to 18 percent lindane.

Lindane is a broad spectrum insecticide, and is a member of the cyclic organo-chlorinated hydrocarbons. It is used in a wide range of applications including treatment of animals, buildings, man (for ectoparasites), clothing, water (for mosquitoes), plants, seeds, and soil. Lindane is not currently manufactured in the U.S.; all lindane used in the U.S. is imported (U.S. EPA, 1979).

Lindane has a low residence time in the aquatic environment. It is removed by sedimentation, metabolism, and volatilization. Lindane contributes less to aquatic pollution than the other hexachlorocyclohexane isomers (Henderson, et al. 1971).

Lindane is slowly degraded by soil microorganisms (Mathur and Saha, 1975; Tu, 1975, 1976) and is reported to be isomerized to the alpha- and/or delta- isomers in microorganisms and plants (U.S. EPA, 1979), but not in rats (Copeland and Chadwick, 1979). The metabolic pathway in microorganisms is still controversial (Tu, 1975, 1976; Copeland and Chadwick, 1979).

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II. EXPOSURE

A. Water

The contamination of water has occurred principally from direct application of technical hexachlorocyclohexane (HCH) or lindane to water for control of mosquitoes or from the use of HCH in agriculture and forestry; and to a lesser extent from occasional contamination of wastewater from manufacturing plants (U.S. EPA, 1979).

Lindane has been detected in the finished water of Streator, Illinois, at a concentration of 4 µg/l (U.S. EPA, 1975).

B. Food

The daily intake of lindane has been reported at 1 to 5 µg/kg body weight and the daily intake of all other HCH isomers at 1 to 3 µg/kg body weight (Duggan and Duggan, 1973). The chief sources of HCH residues in the human diet are milk, eggs, and other dairy products (U.S. EPA, 1979) and carrots and potatoes (Lichtenstein, 1959). Seafood is usually a minor source of HCH, probably because of the relatively high rate of dissipation of HCH in the aquatic environment (U.S. EPA, 1979).

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for lindane to be 780 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on measured steady-state bioconcentration studies in bluegills.

C. Inhalation

Traces of HCH have been detected in the air of central and suburban London (Abbott, et al. 1966). Uptake of lindane by inhalation is estimated at 0.002 µg/kg/day (Barney, 1969).

D. Dermal

Lindane has been used to eradicate human ectoparasites, a few adverse reactions have been reported (U.S. EPA, 1979).

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III. PHARMACOKINETICS

A. Absorption

The rapidity of lindane absorption is enhanced by lipid-mediated carriers. Compared to other organochlorine insecticides, lindane is unusually soluble in water which contributes to its rapid absorption and excretion (Herbst and Bodenstein, 1972; U.S. EPA, 1979). Intraperitoneal injections of lindane resulted in 35 percent absorption (Koransky, et al. 1963). Lindane is also absorbed after oral and dermal exposure (U.S. EPA, 1979).

B. Distribution

After administration to experimental animals, lindane was detected in the brain at higher concentrations than in other organs (Laug, 1948; Davidow and Frawley, 1951; Koransky, et al. 1963; Huntingdon Research Center, 1971). At least 75 percent of an intraperitoneal dose of ^{14}C-labeled lindane was consistently found in the skin, muscle, and fatty tissue (Koransky, et al. 1963). Lindane enters the human fetus through the placenta; higher concentrations were found in the skin than in the brain, but never exceeded the corresponding values for adult organs (Poradovsky, et al. 1977; Nishimura, et al. 1977).

C. Metabolism

Copeland and Chadwick (1979) found that lindane did not isomerize in adipose tissues in rats, but noted dechlorination to γ-3,4,5,6-tetrachlorocyclohexene. Some other metabolites reported have been 2,3,4,5,6-pentachloro-2-cyclohexene-1-ol, pentachlorophenol, tetrachlorophenols, and three trichlorophenols (Chadwick, et al. 1975; Engst, et al. 1977), all of which were found in the urine as conjugates (Chadwick and Freal, 1972). Lindane metabolic pathways are still matters of some controversy (Engst, et

al. 1977; Copeland and Chadwick, 1979). Both free and conjugated chlorophenols with the possible exception of pentachlorophenol (Engst, et al. 1977) are far less toxic than lindane (Natl. Acad. Sci., 1977).

D. Excretion

Metabolites of lindane appear to be eliminated primarily as conjugates in the urine. Very little unaltered lindane is excreted (Laug, 1948). Elimination of lindane appears to be rapid after administration ceases (U.S. EPA, 1979).

IV. EFFECTS

A. Carcinogenicity

Nagasaki, et al. (1972b) fed α, β, γ, and δ isomers separately in the diet to mice at levels of 100, 250, and 500 ppm. At termination of the experiment after 24 weeks, multiple liver tumors, some as large as 2.0 centimeters in diameter were observed in all animals given α-HCH at the 500 ppm level. The 250 ppm α-HCH level resulted in smaller nodules, while no lesions were found at levels of 100 ppm. The various dosages did not produce any tumors with respect to the other isomers. Pathomorphological investigations by Didenko, et al. (1973) established that the γ isomer did not induce tumors in mice given intragastric administration at doses of 25 mg/kg twice a week for five weeks.

Hanada, et al. (1973) fed six-week-old mice a basal diet of 100, 300, and 600 ppm t-HCH and the α, β, γ isomers for a period of 32 weeks. After 38 weeks, liver tumors were found in 76.5 percent of the males and 43.5 percent of the females fed t-HCH, indicating males were more highly susceptible to HCH-induced tumors than females. Multiple nodules were found in the liver, although no peritoneal invasion or distinct metastasis was found. The β-isomer-treated animals had no tumors.

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Goto, et al. (1972) essentially confirmed the findings of the above study using diets containing 600 ppm levels over a 26 week period. The combination of β-, γ-, or δ-HCH with the highly carcinogenic action of α-HCH revealed no synergistic or antagonistic effect on the production of tumors by α-HCH for dd strains of mice (Ito, et al. 1973). Kashyap, et al. (1979) found that γ-HCH (14 percent lindane) at 100 ppm levels in the diet or at 10 mg/kg/day caused liver and lymphoreticular tissue tumors in both male and female mice after 45 weeks. Application by skin painting had no effect.

The National Cancer Institute conducted a bioassay for the possible carcinogencity of δ-HCH to Osborne-Mendel rats and B6C3F1 mice. Administration continued for 80 weeks at two dose levels: time-weighted average dose for male rats was 236 and 472 ppm; for female rats, 135 and 275 ppm; and for all mice, 80 and 160 ppm. No statistically significant incidence of tumor occurrence was noted in any of the experimental rats as compared to the controls. At the lower dose concentration in male mice, the incidence of hepatocellular carcinoma was significant when compared to the controls, but not significant in the higher dose males. "Thus, the incidence of hepatocellular carcinoma in male mice cannot clearly be related to treatment." The incidence of hepatocellular carcinoma among female mice was not significant. Consequently, the carcinogenic activity of γ-HCH in mice is questionable (Natl. Cancer Inst., 1977).

B. Mutagenicity

Some alterations in mitotic activity and the karyotype of human lymphocytes cultured with lindane at 0.1 to 10 mg/ml have been reported (Tsoneva-Maneva, et al. 1971). γ-HCH was mutagenic in assays using Salmonella typhimurium with metabolic activation, the host-mediated assay, and the

dominant lethal assay in rats. Other reports indicate that it does not have significant mutagenic activity (U.S. EPA, 1979; Buselmair, et al. 1973).

C. Teratogenicity

Lindane given in the diet during pregnancy at levels of 12 or 25 mg/kg body weight/day did not produce teratogenic effects in rats (Mametkuliev, 1978; Khera, 1979).

D. Other Reproductive Effects

Chronic lindane feeding in a study of four generations of rats increased the average duration of pregnancy, decreased the number of births, increased the proportion of stillbirths, and delayed sexual maturation in F2 and F3 females. In addition, some of the F1 and F2 animals exhibited spastic paraplegia (Petrescu, et al. 1974).

In rats and rabbits, lindane given in the diet during pregnancy increased postimplantation death of embryos (Mametkuliev, 1978; Palmer, et al. 1978). Testicular atrophy has been observed in rats and mice (National Cancer Institute, 1977; Nigam, et al. 1979).

E. Chronic Toxicity

Irritation of the central nervous system with other toxic side effects (nausea, vomiting, spasms, weak respiration with cyanosis and blood dyscrasia) have been reported after prolonged or improper use of Hexicid (1 percent lindane) for the treatment of scabies on humans (Lee, et al. 1976).

In chronic studies with rats given lindane in oil, liver cell hypertrophy (fat degeneration and necrosis) and nephritic changes were noted at higher doses (Fitzhugh, et al. 1950; Lehman, 1952a,b). Rats inhaling lindane (0.78 mg/m^3) for 7 hours, 5 days a week for 180 days showed liver cell enlargement but showed no clinical symptoms or other abnormalities (Heyroth, 1952). The addition of 10 ppm lindane to the diet of rats for one

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or two years decreased body weight after five months of treatment and altered ascorbic acid levels in urine, blood, and tissues (Petrescu, et al. 1974). Dogs chronically exposed to lindane in the diet had friable and slightly enlarged livers (Rivett, et al. 1978).

F. Other Relevant Information

Lindane is a convulsant and is the most acutely toxic isomer of hexachlorocyclohexane. The toxic effects of lindane are antagonized by pretreatment with phenobarbitol (Litterst and Miller, 1975) and by treatment with silymarin (Szpunar, et al. 1976), and various tranquilizers (Ulmann, 1972).

V. AQUATIC TOXICITY

A. Acute Toxicity

The range of adjusted LC_{50} values for one flow-through and 24 static bioassays for lindane in freshwater fish ranged from 1 µg/l for the brown trout Salmo trutta (Macek, et al. 1970) to 83 µg/l for the goldfish (Carassius auratus), and represents the results of tests on 16 freshwater fish species (U.S. EPA, 1979). Zebrafish (Brachydanio rerio) showed an LC_{50} value of 120 µg/l but rainbow trout (Salmo gairdneri) exhibited respiratory distress at 40 µg/l (Slooff, 1979). Among eight species of freshwater invertebrates studied with lindane, stoneflies (Pteronarcys californica) and three species of crustaceans: scuds (Gammarus lacustris and G. faciatus) and sowbugs (Ascellus brevicaudus) were most sensitive, with adjusted LC_{50} values ranging from 4 to 41 µg/l. Three species of cladocerans (Daphnia pulex, D. magna and Simocephalus serralatus) were most resistant with LC_{50} values of 390 to 745 µg/l. The midge (Chironomus tentans) was intermediate in sensitivity with LC_{50} values of 175 µg/l (U.S. EPA, 1979).

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Among eight species of marine fish tested in static bioassays with lindane, the Atlantic silversides (Menidia menidia) was most sensitive, with an acute LC_{50} of 9 µg/l (Eisler, 1970), while the striped mullet (Mugil cephalus) was reported as having an acute static LC_{50} of 66.0 µg/l (U.S. EPA, 1979). The results of six flow-through assays on five species of marine fish revealed that the striped bass (Morone saxatilis) was most sensitive with an acute LC_{50} of 7.3 µg/l (Korn and Earnest, 1974); and the longnose killifish (Fundulus similis) was most resistant with a reported LC_{50} of 240 µg/l. Acute studies with six species of marine invertebrates showed these organisms to be extremely sensitive to lindane, with LC_{50} values ranging from 0.17 µg/l for the pink shrimp, Panaeus duorarum (Schimmel, et al. 1977), to 8.5 µg/l for the grass shrimp (Palaemonetes vulgaris).

B. Chronic

A chronic value of 14.6 µg/l was obtained for lindane in a life-cycle assay of the freshwater fathead minnow (Pimephales promelas). Chronic values of 3.3, 6.1, and 14.5 µg/l were obtained for three freshwater invertebrates, Chironomus tentans, Gammarus fasciatus, and Daphnia magna (Macek, et al. 1976). No marine chronic studies were available.

C. Plant Effects

For freshwater algae, Scenedesmus acutus, the effective concentration for growth inhibition was 1,000 µg/l. Effective concentrations for marine phytoplankton communities and the algae, Acetabularia mediterranea, were 1,000 and 10,000 µg/l, respectively. Irreparable damage to Chlorella spec. occurred at concentrations greater than 300 µg/l (Hansen, 1979).

D. Residues

Bioconcentration factors for lindane ranging from 35 to 938 have been obtained for six species of freshwater fish and invertebrates. No bioconcentration factors for lindane have been determined for marine organisms

(U.S. EPA, 1979; Sugiura, et al. 1979). Equilibrium accumulation factors of 429 to 602 were observed at days 2 to 6 after exposure of Chlorella spec. to 10 to 400 µg/l of lindane in aqueous solution (Hansen, 1979).

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

Using the "one-hit" model, the U.S. EPA (1979) has estimated that the water concentration of lindane (gamma-HCH) corresponding to a lifetime cancer risk for humans of 10^{-5} is 54 ng/l, based on the data of Thorpe and Walker (1973) for the induction of liver tumors in male mice.

Tolerance levels set by the U.S. EPA are as follows: 7 ppm for animal fat; 0.3 ppm for milk; 1 ppm for most fruits and vegetables; 0.004 ppm for finished drinking water; and 0.5 mg/m^3 (skin) for air (U.S. EPA, 1979). It is not clear whether these levels are for hexachlorocyclohexane or for lindane.

B. Aquatic

The criterion has been drafted to protect freshwater organisms as a 0.21 µg/l 24-hour average concentration not to exceed 2.9 µg/l. Data are insufficient to draft criterion for the protection of marine life from gamma-hexachlorocyclohexane (lindane).

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No. 114

Hexachlorocyclopentadiene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

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HEXACHLOROCYCLOPENTADIENE

Summary

Hexachlorocyclopentadiene (HEX) is used as a chemical intermediate in the manufacture of chlorinated pesticides. Evidence is not sufficient to categorize this compound as a carcinogen or non-carcinogen; HEX was not mutagenic in either short-term *in vitro* assays or a mouse dominant lethal study. Teratogenic effects were not observed in rats receiving oral doses of HEX during gestation.

The reported 96-hour LC_{50} value for the fathead minnow under static and flow-through conditions using larval and adult fish ranges from 7.0 µg/l to 104 µg/l. The chronic value for fish in an embryo-larval test is 2.6 µg/l.

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HEXACHLOROCYCLOPENTADIENE

I. INTRODUCTION

Hexachlorocyclopentadiene (HEX; C_5Cl_6) is a pale to greenish-yellow liquid. Other physical properties include: molecular weight, 272.77; solubility in water, 0.805 mg/l; and vapor pressure, 1 mm Hg at 78-79°C. HEX is a highly reactive compound and is used as a chemical intermediate in the manufacture of chlorinated pesticides (Kirk-Othmer, 1964). Recent government bans on the use of chlorinated pesticides have restricted the use of HEX as an intermediate to the endosulfan and decachlorobi-2,4-cyclopentadiene-1-yl industries. Currently, the major use of HEX is as an intermediate in the synthesis of flame retardants (Sanders, 1978; Kirk-Othmer, 1964). Production levels of HEX approximate 50 million pounds per year (Bell, et al. 1978).

Environmental monitoring data for HEX are lacking, except for levels measured in the vicinity of industrial sites. The most likely route of entry of HEX into the environment arises from its manufacture or the manufacture of HEX-containing products. Small amounts of HEX are present as impurities in pesticides made from it; some HEX has undoubtedly entered the environment via this route.

HEX appears to be strongly adsorbed to soil or soil components, although others have reported its volatilization from soil (Rieck, 1977a, 1977b). HEX degrades rapidly by photolysis, giving water-soluble degradation products (Natl. Cancer Inst., 1977). Tests on its stability towards hydrolysis at ambient temperature indicated a half-life of about 11 days at pH3-6, which was reduced to 6 days at pH 9.

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II. EXPOSURE

A. Water

HEX has been detected in water near points of industrial discharge at levels ranging from 0.156 to 18 mg/l (U.S. EPA, 1979). Other than this, there is little information concerning HEX concentrations in surface or drinking waters. Due to its low solubility, photolability, and tendency to volatize, one would not expect HEX to remain in flowing water.

B. Food

HEX has been identified in a few samples of fish taken from waters near the Hooker Chemical Plant in Michigan (Spehar, et al. 1977). No reports concerning HEX contamination of other foods could be located.

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor of HEX for the edible portions of fish and shellfish consumed by Americans to be 3.2. This estimate is based on measured steady-state bioconcentration studies in fathead minnows.

C. Inhalation

The most significant chronic exposure to HEX occurs among persons engaged directly in its manufacture and among production workers fabricating HEX-containing products. Inhalation is the primary mode of exposure to HEX in the event of accidental spills, illegal discharges, or occupational situations.

III. PHARMACOKINETICS

A. Absorption

Kommineni (1978) found in rats that HEX is absorbed through the squamous epithelium of the nonglandular part of the stomach, causing necrotic changes, and that the major route of elimination of HEX is through the lungs. This information is based on morphological changes in rats

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administered HEX by gavage. Further study with guinea pigs showed that HEX was absorbed through the skin; but, unlike the rat stomach, the squamous epithelium of these animals did not undergo necrotic changes.

B. Distribution

The tissues of four rats administered single oral doses of HEX retained only trace amounts of the compound after 7 days (Mehendale, 1977). For example, approximately 0.5 percent of the total dose was retained in the kidney and less than 0.5 percent in the liver. Other organs and tissues - fat, lung, muscle, blood, etc. - contained even less HEX. Tissue homogenates from rats receiving injections of ^{14}C-HEX showed that 93 percent of the radioactivity in the kidney and 68 percent in the liver were associated with the cytosol fraction (Mehendale, 1977).

C. Metabolism

At least four metabolites were present in the urine of rats administered HEX (Mehendale, 1977). Approximately 70 percent of the metabolites were extractable using a hexane:isopropanol mixture.

D. Excretion

Mehendale (1977) found that approximately 33 percent of the total dose of HEX administered to rats via oral intubation was excreted in the urine after 7 days. About 87 percent of that (28.7 percent of the total dose) was eliminated during the first 24 hours. Fecal excretion accounted for 10 percent of the total dose; nearly 60 percent of the 7 day fecal excretion occurred during the first day. These findings suggest that elimination of HEX may occur by routes other than urine and feces, and it has been postulated that a major route of excretion may be the respiratory tract.

Whitacre (1978) did not agree with the study by Mehendale (1977). This recent study of HEX excretion from mice and rats showed that excretion was mainly by the fecal route with no more than 15 percent in the urine.

Approximately nine percent of an injected dose of HEX was excreted in the bile in one hour (Mehendale, 1977). Because this quantity is equivalent to that excreted in the feces over seven days, enterohepatic circulation of this compound is probable.

IV. EFFECTS

A. Carcinogenicity

Only one *in vitro* test of HEX for carcinogenic activity could be located. Litton Bionetics (1977) reported the results of a test to determine whether HEX could induce malignant transformation in BALB/3T3 cells. HEX was found to be relatively toxic to cells, but no significant carcinogenic activity was reported with this assay.

The National Cancer Institute (1977) concluded that toxicological studies conducted thus far have not been adequate for evaluation of the carcinogenicity of HEX. Because of this paucity of information and HEX's high potential for exposure, HEX has been selected for the NCI's carcinogenesis testing program.

B. Mutagenicity

HEX has been reported to be non-mutagenic in short-term *in vitro* mutagenic assays (Natl. Cancer Inst., 1977; Industrial Bio-Test Laboratories, 1977; Litton Bionetics, 1978a) and in a mouse dominant lethal assay (Litton Bionetics, 1978b).

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C. Teratogenicity

International Research and Development Corporation (1978) studied the effect of oral doses of up to 300 mg/kg/day of HEX administered to rats on days 6 through 15 of gestation. Teratogenic effects were not reported at doses up to 100 mg/kg/day; the highest dosage (300 mg/kg/day) resulted in the death of all rats by day ten of gestation. In this study, elimination via the respiratory tract did not appear to be significant.

D. Other Reproductive Effects

Pertinent information could not be located in the available literature.

E. Chronic Toxicity

There are very few studies concerning the chronic toxicity of HEX in laboratory animals. Naishstein and Lisovskaya (1965) found that daily administration of 1/30 the median lethal dose (20 mg/kg) for 6 months resulted in the death of two of ten animals. The investigators judged the cumulative effects of HEX to be weak; no neoplasms or other abnormalities were reported. Naishstein and Lisovskaya (1965) applied 0.5 to 0.6 ml of a solution of 20 ppm HEX daily to the skin of rabbits for 10 days and found no significant adverse effects from exposure. Treon, et al. (1955) applied 430-6130 mg/kg HEX to the skin of rabbits. Degenerative changes of the brain, liver, kidneys, and adrenal glands of these animals were noted, in addition to chronic skin inflammation, acanthosis, hyperkeratosis, and epilation. Further study by Treon, et al. (1955) revealed slight degenerative changes in the liver and kidney of guinea pigs, rabbits, and rats exposed to 0.15 ppm HEX for daily seven-hour periods over approximately seven months. Four of five mice receiving the same dosage died within this period.

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There is virtually no information regarding the human health effects of chronic exposure to HEX. According to Hooker's material safety data sheet for HEX, (1972) acute exposure to the compound results in irritation of the eyes and mucous membranes, causing lacrimation, sneezing, and salivation. Repeated contact with the skin can cause blistering and burns, and inhalation can cause pulmonary edema. Ingestion can cause nausea, vomiting, diarrhea, lethargy, and retarded respiration.

V. AQUATIC TOXICITY

A. Acute Toxicity

The reported 96-hour LC_{50} values for the fathead minnow (Pimephales promelas) under static and flow-through conditions with larval and adult fish range from 7.0 µg/l to 104 µg/l. The effect of water hardness is minimal (Henderson 1956; U.S. EPA, 1978). There are no reports of studies of the acute toxicity of HEX on saltwater organisms.

B. Chronic Toxicity

In the only chronic study reported, the lowest chronic value for the fat- head minnow (embryo-larval) is 2.6 µg/l (U.S. EPA, 1978).

C. Plant Effects

Pertinent information could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

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A. Human

The Occupational Safety and Health Administration has not set a standard for occupational exposure to HEX. The American Conference of Governmental Industrial Hygienists has adopted a threshold limit value (TLV) of 0.01 ppm (0.11 mg/m^3) and a short term exposure limit of 0.03 ppm (0.33 mg/m^3) (ACGIH, 1977).

The draft ambient water quality criterion for HEX is 1.0 µg/l (U.S. EPA, 1979).

B. Aquatic

For HEX, the draft criterion to protect freshwater aquatic life is 0.39 µg/l as a 24-hour average, not to exceed 7.0 µg/l at any time (U.S. EPA, 1979). Criteria have not been proposed for saltwater species because of insufficient data.

HEXACHLOROCYCLOPENTADIENE

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No. 115

Hexachloroethane

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

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HEXACHLOROETHANE

SUMMARY

Results of a National Cancer Institute (NCI) carcinogenesis bioassay showed that hexachloroethane produced an increase in hepatocellular carcinoma incidence in mice.

Testing of hexachloroethane in the Ames Salmonella assay showed no mutagenic effects. No teratogenic effects were observed following oral or inhalation exposure of rats to hexachloroethane, but some toxic effects on fetal development were observed.

Toxic symptoms produced in humans following hexachloroethane exposure include central nervous system depression and liver, kidney, and heart degeneration.

Hexachloroethane is one of the more toxic of the chlorinated ethanes reviewed for aquatic organisms with marine invertebrates appearing to be the most sensitive organisms studied. This chlorinated ethane also had the greatest bioconcentration factor, 139 for bluegill sunfish, observed in this class of compounds.

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HEXACHLOROETHANE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Chlorinated Ethanes (U.S. EPA, 1979a).

The chloroethanes are hydrocarbons in which one or more of the hydrogen atoms are replaced by chlorine atoms. Water solubility and vapor pressure decrease with increasing chlorination, while density and melting point increase. Hexachloroethane (Perchloroethane; M.W. 236.7) is a solid at room temperature with a boiling point of 186^{o}C, specific gravity of 2.091; and is insoluble in water (U.S. EPA, 1979a).

The chloroethanes are used as solvents, cleaning and degreasing agents, and in the chemical synthesis of a number of compounds. Hexachloroethane does not appear to be commercially produced in the U.S., but 730,000 kg were imported in 1976. (U.S. EPA, 1979a).

The chlorinated ethanes form azeotropes with water (Kirk and Othmer, 1963). All are very soluble in organic solvents (Lange, 1956). Microbial degradation of the chlorinated ethanes has not been demonstrated (U.S. EPA, 1979a).

The reader is referred to the Chlorinated Ethanes Hazard Profile for a more general discussion of chlorinated ethanes (U.S. EPA, 1979b).

II. EXPOSURE

The chloroethanes are present in raw and finished waters due primarily to industrial discharges. Small amounts of the chloroethanes may be formed by chlorination of drinking water or treatment of sewage. Air levels are produced by evaporation of volatile chloroethanes.

Sources of human exposure to chloroethanes include water, air, contaminated foods and fish, and dermal absorption. Fish and shellfish have shown

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levels of chloroethanes in the nanogram range (Dickson and Riley, 1976). Information on the levels of hexachloroethane in foods is not available.

U.S. EPA (1979a) has estimated the weighted average bioconcentration factor for hexachloroethane to be 320 for the edible portion of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficient.

III. PHARMOKINETICS

Pertinent data could not be located in the available literature on hexachloroethane for absorption, distribution, metabolism, and excretion. However, the reader is referred to a more general treatment of chloroethanes (U.S. EPA, 1979b) which indicates rapid absorption of chloroethanes following oral or inhalation exposure; widespread distribution of the chloroethanes through the body; enzymatic dechlorination and oxidation to the alcohol and ester forms; and excretion of the chloroethanes primarily in the urine and in expired air.

IV. EFFECTS

A. Carcinogencitiy

Results of an NCI carcinogenensis bioassay for hexachloroethane showed that oral administration of the compound produced an increase in the incidence of hepatocellular carcinoma in mice. No statistically significant tumor increase was seen in rats.

B. Mutagenicity

The testing of hexachloroethane in the Ames Salmonella assay or in a yeast mutagenesis system failed to show any mutagenic activity (Weeks, et al. 1979).

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C. Teratogenicity

Teratogenic effects were not observed in pregnant rats exposed to hexachloroethane by inhalation or intubation (Weeks, et al. 1979).

D. Other Reproductive Effects

Hexachloroethane administered orally to pregnant rats decreased the number of live fetuses per litter and increased the fetal resorption rate (Weeks, et al. 1979).

E. Chronic Toxicity

Toxic symptoms produced in humans following hexachloroethane exposure include liver, kidney, and heart degeneration, and central nervous system depression (U.S. EPA, 1979a).

Animal studies have shown that chronic exposure to hexachloroethane produces both hepatotoxicity and nephrotoxicity (U.S. EPA, 1979a).

V. AQUATIC TOXICITY

A. Acute Toxicity

Among freshwater organisms, the bluegill sunfish (Lepomis macrochirus) was reported to have the lowest sensitivity to hexachloroethane, with a 96-hour static LC_{50} value of 980 µg/l. The 48-hour static LC_{50} value of the freshwater Cladoceran (Daphnia magna) was reported as 8,070 µg/l (U.S. EPA, 1978). For the marine fish, the sheepshead minnow (Cyprinodon variegatus), a 96-hour LC_{50} value of 2,400 µg/l was reported from a static assay. The marine mysid shrimp (Mysidopsis bahia) was the most sensitive aquatic organism tested, with a 96-hour static LC_{50} value of 940 µg/l (U.S. EPA, 1978).

B. Chronic Toxicity

Pertinent data could not be located in the available literature.

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C. Plant Effects

For the freshwater algae, Selenastrum capricornutum, the 96-hour EC_{50} effective concentrations based on chlorophyll and cell number were 87,000 and 93,200 µg/l for chlorophyll a production and cell growth, respectively. The marine algae, Skeletonema costatum, was much more sensitive, with effective concentrations from 7,750 to 8,570 µg/l being reported.

D. Residues

A bioconcentration factor of 139 was obtained for the freshwater bluegill sunfish (U.S. EPA, 1979a).

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

By applying a linear, non-threshold model to the data from the NCI bioassay for carcinogenesis, the U.S. EPA (1979a) has estimated the level of hexachloroethane in ambient water that will result in an additional risk of 10^{-5} to be 5.9 µg/l.

The eight-hour TWA exposure standard established by OSHA for hexachloroethane is 1 ppm.

B. Aquatic Toxicity

The proposed criterion to protect freshwater aquatic life is 62 µg/l as a 24-hour average and should not exceed 140 µg/l at any time. The drafted criterion for saltwater aquatic life is a 24-hour average concentration of 7 µg/l not to exceed 16 µg/l at any time.

HEXACHLOROETHANE

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No. 116

Hexachlorophene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
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116-1
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DISCLAIMER

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HEXACHLOROPHENE

Summary

Oral, dermal, and subcutaneous administration of hexachlorophene in animal studies has failed to show significant carcinogenic effects.

Mutagenic effects of hexachlorophene exposure have been reported in one study which indicated increased chromosome aberrations in rats. Testing of hexachlorophene in the host mediated assay or the dominant lethal assay did not produce positive effects.

Several reports have indicated that hexachlorophene may produce some teratogenic and embryotoxic effects. A three generation feeding study in rats failed to show any teratogenic activity. Hexachlorophene has shown some adverse effects on male reproductive performance.

Chronic administration of hexachlorophene has produced central nervous system effects and muscular paralysis.

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I. INTRODUCTION

Hexachlorophene ($C_{13}H_6O_2Cl_6$, molecular weight 406.9) is a white powder which melts between 166°C and 167°C. The compound is practically insoluble in water but is soluble in ethanol, ether, and other organic solvents. Under alkaline conditions, hexachlorophene forms water-soluble salts (IARC, 1979).

The principle uses of hexachlorophene have been for the manufacture of germicidal soaps, as a topical anti-infective agent for humans, as a veterinary anti-helminthic, for disinfection of hospital equipment, and as a broad-spectrum soil fungicide (IARC, 1979). Limitation of drugs and cosmetics containing hexachlorophene was instituted by the FDA in 1972.

Commercial hexachlorophene produced from 2,4,5-trichlorophenol contains less than 15 µg/kg of 2,3,7,8-tetrachlorodibenzo-para-dioxin (IARC, 1979).

II. EXPOSURE

There are no available estimates on daily exposure levels of humans to hexachlorophene from air, water, or food.

Water monitoring studies have detected hexachlorophene in two finished drinking water samples (Shackelford and Keith, 1976) and in effluents of sewage treatment plants at levels of 3.2 to 44.3 µg/l (Sims and Pfaender, 1975), as well as in creek sediments (9.3 to 377 µg/kg).

Data on hexachlorophene levels in aquatic organisms indicate that the compound is bioaccumulated (Sims and Pfaender, 1975).

Hexachlorophene has been detected in human milk at levels up to 9 µg/l (West, et al. 1975). Blood levels of the compound in users of soap containing hexachlorophene have been reported (0.02 to 0.14 mg/l blood) (Butcher, et al. 1973); blood levels fall after use is discontinued.

A 1974 survey by NIOSH indicated that exposure to hexachlorophene was primarily in hospitals, sanitariums, and convalescent homes (IARC, 1979).

III. PHARMACOKINETICS

A. Absorption

Systemic toxicity following dermal application or ingestion of hexachlorophene indicates that the compound is absorbed through the skin and the gastrointestinal tract (AMA Drug Evaluations, 1977).

B. Distribution

Whole-body autoradioigraphs of the murine fetus during late gestation following administration of labelled hexachlorophene indicate an even distribution pattern of the compound . The compound crosses the placenta; fetal retention increases during the course of pregnancy (Brandt, et al. 1979). Hexachlorophene has been detected in human adipose samples at levels of 0.80 µg/kg (Shafik, 1973).

C. Metabolism

Hexachlorophene is metabolized by the liver, producing a glucuronide conjugate. The clearance of blood hexachlorophene is dependent on this hepatic activity (Klaassen, 1979).

D. Excretion

Within three hours of hexachlorophene administration to rats, 50 percent of the initial dose was excreted in the bile (Klaassen, 1979). Oral administration of the compound to a cow resulted in excretion of 63.8 percent of the initial dose in the feces and 0.24 percent in the urine (St. John and Lisk, 1972).

IV. EFFECTS

A. Carcinogenicity

The lifetime dermal application of 25-percent and 50-percent solutions of hexachlorophene to mice failed to produce significant carcinogenic effects (Stenback, 1975); the levels of compound used caused high toxicity. Rudali and Assa (1978) were unable to produce carcinogenic effects in mice by lifetime feeding or subcutaneous injection at birth of hexachlorophene. Oral lifetime feeding of hexachlorophene to rats (17 to 150 ppm) also failed to show carcinogenic effects (NCI, 1978).

B. Mutagenicity

Single intraperitoneal injections of 2.5 or 5.0 mg/kg hexachlorophene failed to induce dominant lethal mutations in mice (Arnold, et al. 1975).

Desi, et al. (1975) have reported that hexachlorophene administered to rats produced chromosome aberrations (dose and route not specified).

C. Teratogenicity

Kennedy, et al. (1975a) reported that the fetuses of pregnant rats exposed to hexachlorophene at 30 mg/kg on days 6 to 15 of gestation show a low frequency of eye defects and skeletal abnormalities (angulated ribs). Fetuses of rabbits exposed to this compound at 6 mg/kg on days 6 to 18 of gestation showed a low incidence of skeletal irregularities, but no soft tissue anomalies (Kennedy, et al. 1975a). A three-generation feeding study of hexachlorophene to rats at levels of 12.5 to 50 ppm did not show teratogenic effects (Kennedy, et al. 1975b).

A single retrospective Swedish study on infants born to nurses regularly exposed to antiseptic soaps containing hexachlorophene has suggested that the incidence of malformations in this infant population is increased (Halling, 1979).

D. Other Reporductive Effects

Gellert, et al. (1978) have reported that male neonatal rats washed for eight days with three percent hexachlorophene solutions showed as adults a decreased fertility due to inhibited reflex ejaculation.

Oral administration of hexachlorophene to rats has been reported to produce degeneration of spermatogenic cells (Casaret and Doull, 1975). Subcutaneous injection of hexachlorophene to mice at various periods of gestation produced increased fetal resorptions (Majundar, et al. 1975).

E. Chronic Toxicity

Administration of hexachlorophene by gavage (40 mg/kg) produced hind leg paralysis and growth impairment after two to three weeks (Kennedy and Gordon, 1976). Histological examination showed generalized edema or status spongiosus of the white matter of the entire central nervous system. These gross effects and histopathological lesions have been reported to be reversible (Kennedy, et al. 1976).

Central nervous system effects in humans following chronic exposure to hexachlorophene include diplopia, irritability, weakness of lower extremities, and convulsions (Sax, 1975).

V. AQUATIC TOXICITY

A. Acute and Chronic Toxicity and Plant Effects

Pertinent data were not found in the available literature.

B. Residues

Sims and Pfaender (1975) found levels of hexachlorophenol in aquatic organisms ranging from 335 ppb in sludge worms to 27,800 ppb in water boatman (Sigara spp.).

VI. EXISTING GUIDELINES

A. Human

Hexachlorophene is permitted as a preservative in drug and cosmetic products at levels up to 0.1 percent (USFDA, 1972).

B. Aquatic

Pertinent data were not found in the available literature.

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No. 117

Hydrofluoric Acid

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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117-1

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

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117-2

HYDROFLUORIC ACID

Summary

Hydrofluoric acid (HF) has produced mutagenic effects in plants and Drosophila, and lymphocyte chromosome aberrations in rats. Chromosome effects were not observed in mice following sub-chronic inhalation exposure to the compound.

No data are avilable on the possible carcinogenic or teratogenic effects of HF.

Chronic exposure to the compound has produced skeletal fluorosis, dental mottling and pulmonary function impairment.

One short-term bioassay test demonstrated that a concentration of 50,000 µg/l HF was lethal to bluegill sunfish in one hour.

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HYDROFLUORIC ACID

I. INTRODUCTION

Hydrofluoric acid (CAS registry number 7664-39-3) (HF) is a colorless, clear, fuming corrosive liquid made by treating fluorspar (CaF_2) with sulfuric acid. An unusual property of HF is that it will dissolve glass or any other silica-containing material. It has the following physical and chemical properties (Windholz, 1976; Hawley, 1971; Weast, 1972):

	Pure	Constant Boiling
Formula:	HF	HF/H_2O
Molecular Weight:	20.01	---
Melting Point:	-83.55°C	---
Boiling Point:	19.51°C	---
Density:	0.987	1.15 - 1.18
Vapor Pressure:	1 atm @ 19.51°C	
Solubility:	Very soluble in water; soluble in many organic solvents, e.g., benzene, toluene, xylene, etc.	

HF is used in the aluminum industry, for the production of fluorocarbons, for uranium processing, for petroleum alkylation, for the production of fluoride salts, and as a pickling agent for stainless steel. It has many other minor uses (CMR, 1978).

II. EXPOSURE

A. Water

Other than occasional leaks and spills, very small amounts of HF are released into water from manufacturing and production facilities (Union Carbide, 1977; U.S. EPA, 1977a). HF is released into the air from coal

fires (U.S. EPA, 1977b) and from manufacturing and production facilities (Union Carbide, 1977). HF released into the air has a high affinity for water, and it is expected that it will rain out (Fisher, 1976). The amounts of HF in water and the extent of its presence could not be determined from the available literature. Under alkaline conditions, HF will form aqueous salts.

B. Food

Pertinent data were not found in the available literature.

C. Inhalation

HF occurs in the atmosphere from coal fires and from manufacturing and production facilities (see above), as well as from the photochemical reaction of CCl_2F_2 with NO and humid air (Saburo, et al. (1977). It is present in the stratosphere (Zander, et al. 1977; Drayson, et al. 1977; Farmer and Raper, 1977). The extent and amounts of HF in the atmosphere could not be determined from the available literature.

D. Dermal

Pertinent data were not found in the available literature.

III. PHARMACOKINETICS

A. Absorption

The major route of HF absorption is by the respiratory system; penetration of liquefied anhydrous HF through the skin has been reported (Burke, et al. 1973). Fatal inhalation of HF fumes resulted in a blood fluoride level of 0.4 mg/100 ml (Greendyke and Hodge, 1964), while skin penetration of anhydrous HF produced a maximum blood fluoride concentration of 0.3 mg/100 ml (Burke, et al. 1973). These levels are 100-fold higher

than normal serum fluoride levels (Hall et al. 1972). Forty-five percent of fluoride present in the air in gaseous or particulate form is absorbed on inhalation (Dinman, et al. 1976).

B. Distribution

Absorbed fluoride is deposited mainly in the skeleton and teeth; it is also found in soft tissues and body fluids (NAS, 1971; NIOSH, 1975; NIOSH, 1976). Fluoride reaches fetal circulation via the placenta and is deposited in the fetal skeleton (NAS, 1971).

Fluoride deposition in bone is not irreversible (NAS, 1971). However, laboratory animals chronically exposed to HF gas retained abnormally high levels of fluoride in the skeleton for up to 14 months after exposure (Machle and Scott, 1935).

C. Metabolism

The physiological or biochemical basis of fluoride toxicity has not been established, although it appears that enzymes involved in vital functions are inhibited by fluoride (NAS, 1971). Examination of the data of Collins, et al. (1951) indicates that metabolism of absorbed fluoride is the same whether it is inhaled as a particulate inorganic or gas (as HF) (NIOSH, 1976).

D. Excretion

Fluoride is excreted in the urine, feces and sweat, and in trace amounts in milk, saliva, hair and probably tears. Data are lacking regarding loss of fluoride by expired breath (NAS, 1971).

The primary route of fluoride elimination is through the urine. The urinary fluroide concentration is influenced by factors such as total absorption, the form of fluoride absorbed, frequency of exposure and general

health (NAS, 1971). It is recognized that urinary fluoride levels are directly related to the concetration of absorbed fluoride (NAS, 1971).

In a relatively unexposed person, about one-half of an acute dose of fluoride is excreted within 24 hours in the urine, and about one-half is deposited in the skeleton (NAS, 1971).

IV. EFFECTS

A. Carcinogenicity

Pertinent data were not found in the available literature.

B. Mutagenicity

Mohamed (1968) has reported various aberrations in second generation tomato plants following parenteral treatment with HF at 3 $\mu g/m^3$. These results could not be duplicated by Temple and Weinstein (1976).

Rats inhaling 0.1 mg HF/m^3 chronically for two months were reported to develop lymphocyte chromosomal aberrations; aberrations could not be detected in sperm cells of mice administered the same levels of HF (Voroshilin, et al. 1973).

Weak mutagenic effects in the offspring of Drosophila exposed to air bubbled through 2.5 percent HF have been reported (Mohamed, 1971).

C. Teratogenicity

Pertinent data were not found in the available literature.

D. Other Reproductive Effects

Reduced fertility in Drosophila and decreased egg hatch have been reported following exposure to 2.9 ppm HF (Gerdes, et al. 1971).

E. Chronic Toxicity

Among the adverse physiologic effects of long-term exposure to HF are skeletal fluorosis, dental mottling and pulmonary impairment (NAS, 1971; NIOSH, 1975; NIOSH, 1976). Skeletal fluorosis is characterized by increased

bone density, especially in the pelvis and spinal column, restricted spinal motion, and ossification of ligaments. Nasal irritation, asthma or shortness of breath, and in some cases pulmonary fibrosis are associated with HF-induced pulmonary distress (NIOSH, 1976). Digestive disturbances have also been noted (NIOSH, 1976). Fluoride-induced renal pathology has not been firmly established in man (Adler, et al. 1970). Causal relationships in industrial exposures are difficult to determine because exposure often involves other compounds in addition to fluorides (NIOSH, 1976).

Laboratory animals chronically exposed to 15.2 mg HF/m^3 developed pulmonary, kidney and hepatic pathology (Machle and Kitzmiller, 1935; Machle, et al. 1934), while animals exposed to 24.5 mg HF/m^3 developed lung edema (Stokinger, 1949). Testicular pathology was also observed in dogs at 24.5 mg HF/m^3 (Stokinger, 1949). Several animal studies have demonstrated that inhalation of HF increased fluoride deposition in the bones (NIOSH, 1976).

F. Other Relevant Information

Fluoride has anticholinesterase character which, in conjunction with the reduction in plasma calcium observed in fluoride intoxication, may be responsible for acute nervous system effects (NAS, 1971). The severe pain accompanying skin injury from contact with 10 percent HF has been attributed to immobilization of calcium, resulting in potassium nerve stimulation (Klauder, et al 1955).

Inhibition of enolase, oxygen uptake, and tetrazolium reductase activity has been demonstrated <u>in vitro</u> from application of HF to excised guinea pig ear skin (Carney, et al. 1974).

V. AQUATIC TOXICITY

A. Acute Toxicity

McKee and Wolf (1963) reported that HF was toxic to fish (unspecified at concentrations ranging from 40,000 to 60,000 µg/l. Bonner and Morgan (1976) observed that 50,000 µg/l HF was lethal to bluegill sunfish (Lepomis macrochirus) in one hour.

B. Chronic Toxicity, Plant Effects, and Residue

Pertinent data were not found in the available literature.

C. Other Relevant Information

Bonner and Morgan (1976) observed a marked increase in the opercular "breathing" rate of bluegill sunfish exposed to a concentration of 25,000 ug/l for four hours. The fish recovered within three days.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

In 1976, NIOSH proposed a workplace environmental limit for HF of 2.5 mg/m^3 (3 ppm) as a time-weighted average to provide protection from the effects of HF over a working lifetime (NIOSH, 1976). A ceiling limit of 5 mg HF/m^3 based on 15-minute exposures was also recommended to prevent acute irritation from HS (NIOSH, 1976).

B. Aquatic

Pertinent data were not found in the available literature.

HYDROFLUORIC ACID

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117-12

No. 118

Hydrogen Sulfide

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

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Hydrogen Sulfide

Summary

Pertinent information could not be located on the carcinogenicity, mutagenicity, or teratogenicity of H_2S.

Hydrogen sulfide is very toxic to humans via inhalation and has been reported to cause death at concentrations of 800 to 1000 ppm.

Hydrogen sulfide is reported to be very toxic to fish with toxic effects resulting from 1 to 100 ppm.

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T312

I. INTRODUCTION

Hydrogen sulfide (H_2S; CAS No. 7783064) is a colorless flammable gas with a rotten egg odor. It has the following physical properties:

Formula	H_2S
Molecular Weight	34.08
Melting Point	-85.5°C
Boiling Point	-60.4°C
Density	1.539 gram per liter at 0°C
Vapor Pressure	20 atm. at 25.5°C

Hydrogen sulfide is soluble in water, alcohol, and glycerol (ITII, 1976). Hydrogen sulfide is a flammable gas and the vapor may travel considerable distance to a source of ignition and flash back.

Hydrogen sulfide and other sulfur compounds occur to some extent in most petroleum and natural-gas deposits. Very substantial quantities of this gas are liberated in coking operations or in the production of manufactured gases from coal (Standen, 1969). Hydrogen sulfide is used to produce substantial tonnages of elemental sulfur, sulfuric acid, and a variety of other chemicals. Completely dry hydrogen sulfide, whether gaseous or liquid, has no acidic properties. Aqueous solutions, however, are weakly acidic (Standen, 1969). In 1965, some 5.2 million metric tons of H_2S was recovered from fossil fuels (Standen, 1969).

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II. EXPOSURE

A. Water

Bacterial reduction of sulfates accounts for the occurrence of H_2S in numerous bodies of water, such as the lakes near El Agheila, Libya. Hydrogen sulfide is familiarly formed as a bacterial decomposition product of protein matter, particularly of animal origin (Standen, 1969) and this gas can be found in most sewage treatment plant and their piping systems.

B. Food

H_2S may be formed within the gastrointestinal tract after the ingestion of inorganic sulfide salts or elemental sulfur due to the actions of gastric acid and of colonic bacteria. (Division of Industrial Hygiene, 1941).

C. Inhalation

Wherever sulfur is deposited, pockets of hydrogen sulfide may be encountered, thus it is found at coal, lead, gypsum, and sulfur mines. Crude oil from Texas and Mexico contain toxic quantities of H_2S (Yont and Fowler, 1926). The decay of organic matter gives rise to the production of H_2S in sewers and waste from industrial plants where animals products are handled. Thus, there has been accidental poisoning from H_2S in tanneries, glue factories, fur-dressing and felt-making plants, abattoirs, and beet-sugar factories; for example, in Lowell, Massachusetts five men were poisoned (three died) when sent to repair a street sewer which drained waste from a tannery (Hamilton and Hardy, 1974).

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Hydrogen sulfide is formed in certain industrial processes such as the production of sulfur dyes, the heating of rubber containing sulfur compounds, the making of artificial silk or rayon by viscose process (Hamilton and Hardy, 1974).

D. Dermal

Pertinent information could not be found in the available literature.

III. PHARMACOKINENTICS

A. Absorption

By far the greatest danger presented by hydrogen sulfide is through inhalation, although absorption through the skin has been reported (Patty, 1967).

B. Distribution

Pertinent information could not be found in the available literature.

C. Metabolism and Excretion

Evidence has been obtained for the presence of a sulfide oxidase in mammalian liver (Baxter and Van Reen, 1958; Sörbo, 1960), but important nonenxymatic mechanisms for sulfide detoxication are also recognized. Sulfide tends to undergo spontaneous oxidation to non-toxic products such as polysulfides, thiosulfates or sulfates (Gosselin, 1976).

When free sulfide exists in the circulating blood a certain amount of hydrogen sulfide is excreted in the exhaled breath, this is sufficient to be detected by odor, but the greater portion, however, is excreted in the urine, chiefly as sulfate, but some as sulfide (Patty, 1967).

IV. EFFECTS

A. Carcinogenicity

Pertinent information could not be found in the available literature.

B. Mutagenicity

Pertinent information could not be found in the available literature.

C. Teratogenicity

Pertinent information could not be found in the available literature.

D. Other Reproductive Efforts

Pertinent information could not be found in the available literature.

E. Chronic Toxicity

At low concentrations of hydrogen sulfide (e.g., 50 to 200 ppm) the toxic symptoms are due to local tissue irritation rather than to systemic actions. The most characteristic effect is on the eye, where superficial injury to the conjunctiva and cornea is known to workers in tunnels, caissons, and sewers as "gas eye" (Grant, 1972). More prolonged or intensive exposures may lead to involvement of the respiratory tract with cough, dyspnea and perhaps pulmonary edema. Evidence of severe pulmonary edema has been found at autopsy and in survivors of massive respiratory exposures (Gosselin, 1976). The irritating action has been explained on the basis that H_2S combines with alkali present in moist tissues to form sodium sulfide, a caustic (Sax, 1979). Chronic

poisoning results in headache, inflammation of the conjunctivae and eyelids, digestive disturbances, loss of weight, and general debility (Sax, 1979).

F. Other Relevant Information

Hydrogen sulfide is reported with a maximum safe concentration of 13 ppm (Standen, 1969), although at first this concentration can be readily recognized by its odor, H_2S may partially paralyze the olfactory nerve to the point at which the presence of the gas is no longer sensed. Hamilton and Hardy (1974) report that at a concentration of 150 ppm, the olfactory nerve is paralyzed.

Exposures of 800-1000 ppm may be fatal in 30 minutes, and high concentrations are instantly fatal (Sax, 1979). There are reports of exceptional cases of lasting injury, after recovery from acute poisoning, which point to an irreversible damage to certain cells of the body resulting from prolonged oxygen starvation (Hamilton and Hardy, 1974). Hydrogen sulfide has killed at concentrations as low as 800 ppm (Verschueren, 1974).

V. AQUATIC TOXICITY

A. Acute Toxicity

Verschueren (1974) has reviewed the effects of H_2S on several aquatic organisms. Goldfish have been reported to die at a concentration of 1 ppm after long time exposure in hard water. Verschueren (1974) reports a 96-hour LC50 value of 10 ppm for goldfish. Verschueren also reports on a large number of fresh water fish with toxic effects resulting from exposure

to H_2S at concentrations ranging from 1 to 100 ppm.

Verschueren (1974) reports median threshold limit values for Arthropoda: Asellus, 96-hour at 0.111 mg/l; Crangonyx, 96 hour at 1.07 mg/l; and Gammarus, 96-hour at 0.84 mg/l.

B. Chronic Toxicity, Plant Effects and Residues

Pertinent information could not be located in the available literature.

C. Other Relevant Information

Verschueren (1974) reports that sludge digestion is inhibited at 70-200 mg/l of H_2S in wastewater treatment plants.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The 8-hour, time-weighted average occupational exposure limit for H_2S has been set in a number of countries and are tabled below (Verschueren, 1974):

T.L.V.:	Russia	7 ppm
	U.S.A.	20 ppm "peak"
	Federal German Republic	10 ppm

H_2S is a Department of Transportation flammable and poisonous gas and must be labelled prior to shipment.

B. Aquatic

Maximum allowable concentration of 0.1 mg/l for Class I and Class II waters has been established in Romania and Bulgaria for H_2S (Verschueren, 1974).

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118-10

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No. 119

Indeno (1,2,3-cd)pyrene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated indeno(1,2,3-c,d)pyrene and has found sufficient evidence to indicate that this compound is carcinogenic.

INDENO[1,2,3-cd]PYRENE

Summary

Indeno[1,2,3-cd]pyrene (IP) is a member of the polycyclic aromatic hydrocarbon (PAH) class. Several compounds in the PAH class are well known to be potent animal carcinogens. However, IP is generally regarded as only a weak carcinogen to animals or man. There are no reports available concerning the chronic toxicity of IP. Exposure to IP in the environment occurs in conjunction with exposure to other PAH; it is not known how these compounds may interact in human systems.

There are no reports available concerning standard acute or chronic toxicity tests of this chemical in aquatic organisms.

I. INTRODUCTION

This profile is based primarily on the Ambient Water Quality Criteria Document for Polynuclear Aromatic Hydrocarbons (U.S. EPA, 1979a) and the Multimedia Health Assessment Document for Polycyclic Organic Matter (U.S. EPA, 1979b).

Indeno[1,2,3-cd]pyrene (IP; $C_{22}H_{12}$) is one of the family of polycyclic aromatic hydrocarbons (PAH) formed as a result of incomplete combustion of organic material. Its physical and chemical properties have not been well-characterized.

PAH, including IP, are ubiquitous in the environment. They have been identified in ambient air, food, water, soils, and sediments (U.S. EPA, 1979b). The PAH class contains several potent carcinogens (e.g., benz[b]fluoranthene), weak carcinogens (benz[a]anthracene), and cocarcinogens (e.g., fluoranthene), as well as numerous non-carcinogens (U.S. EPA, 1979b).

PAH which contain more than three rings (such as IP) are relatively stable in the environment and may be transported in air and water by adsorption to particulate matter. However, biodegradation and chemical treatment are effective in eliminating most PAH in the environment. The reader is referred to the PAH Hazard Profile for a more general discussion of PAH (U.S. EPA, 1979c).

II. EXPOSURE

A. Water

Basu and Saxena (1977, 1978) have conducted monitoring surveys of U.S. drinking water for the presence of six representative PAH, including IP. They found the average total level of the six PAH (fluoranthene, benzo[k]fluoranthene, benzo[j]fluoranthene, benzo[a]pyrene, benzo[g,h,i]-perylene, and indeno[1,2,3-cd]pyrene) to be 13.5 ng/l.

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B. Food

Levels of IP are not routinely monitored in food, but it has been detected in foods such as butter and smoked fish (U.S. EPA, 1979a). However, the total intake of all types of PAH through the diet has been estimated at 1.6 to 16 µg/day (U.S. EPA, 1979b). The U.S. EPA (1979a) has estimated the bioconcentration factor of IP to be 15,000 for the edible portion of fish and shellfish consumed by Americans. This estimate is based upon the octanol/water partition coefficient for IP.

C. Inhalation

There are several studies in which IP has been detected in ambient air (U.S. EPA, 1979a). Measured concentrations ranged from 0.03 to 1.34 ng/m^3 (Gordon, 1976; Gordon and Bryan, 1973). Thus, the human daily intake of IP by inhalation of ambient air may be in the range of 0.57 to 25.5 ng, assuming that a human breathes 19 m^3 of air per day.

III. PHARMACOKINETICS

There are no data available concerning the pharmacokinetics of IP, or other PAH, in humans. Nevertheless, some experimental animal results were published on several other PAH, particularly benzo[a]pyrene.

A. Absorption

The absorption rate of IP in humans or other animals has not been studied. However, it is known (U.S. EPA, 1979a) that, as a class, PAH are well-absorbed across the respiratory and gastrointestinal epithelia membranes. The high lipid solubility of compounds in the PAH class supports this observation.

B. Distribution

Based on an extensive literature review, data on the distribution of IP in mammals were not found. However, it is known (U.S. EPA, 1979a) that other PAH are widely distributed throughout the body following their absorption in experimental rodents. Relative to other tissues, PAH tend to localize in body fat and fatty tissues (e.g., breast).

C. Metabolism

The metabolism of IP in animals or man has not been directly studied. However, IP, like other PAH, is most likely metabolized by the microsomal mixed-function oxidase enzyme system in mammals (U.S. EPA, 1979b). Metabolic attack on one or more of the aromatic rings leads to the formation of phenols and isomeric dihydrodiols by the intermediate formation of reactive epoxides. Dihydrodiols are further metabolized by microsomal mixed-function oxidases to yield diol epoxides, compounds which are known to be biologically reactive intermediates for certain PAH. Removal of activated intermediates by conjugation with glutathione or glucuronic acid, or by further metabolism to tetrahydrotetrols, is a key step in protecting the organism from toxic interaction with cell macromolecules.

D. Excretion

The excretion of IP by mammals has not been studied. However, the excretion of closely related PAH is rapid, and occurs mainly via the feces (U.S. EPA, 1979a). Elimination in the bile may account for a significant percentage of administered PAH. It is unlikely that PAH will accumulate in the body as a result of chronic low-level exposures.

IV. EFFECTS

A. Carcinogenicity

IP is regarded as only a weak carcinogen (U.S. EPA, 1979b). LaVoie and coworkers (1979) reported that IP had slight activity as a tumor initiator and no activity as a complete carcinogen on the skin of mice which is known to be highly sensitive to the effects of carcinogenic PAH.

B. Mutagenicity

LaVoie and coworkers (1979) reported that IP gave positive results in the Ames Salmonella assay.

C. Teratogenicity and Other Reproductive Effects

There are no data available concerning the possible teratogenicity or other reproductive effects as a result of exposure to IP. Other related PAH are apparently not significantly teratogenic in mammals (U.S. EPA, 1979a).

V. AQUATIC TOXICITY

Pertinent information could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have not gone through the process of public review; therefore, there is a possibility that these criteria may be changed.

A. Human

There are no established exposure criteria for IP. However, PAH, as a class, are regulated by several authorities. The World Health Organization (1970) has recommended that the concentration of PAH in drinking water (measured as the total of fluoranthene, benz[g,h,i]perylene, benz[b]-fluoranthene, benz[h]fluoranthene, indeno[1,2,3-cd]pyrene, and benz[a]pyrene) not exceed 0.2 µg/l. Occupational exposure criteria have been established

for coke oven emissions, coal tar products, and coal tar pitch volatiles, all of which contain large amounts of PAH, including IP (U.S. EPA, 1979a).

The U.S. EPA (1979a) draft recommended criteria for PAH in water are based upon the extrapolation of animal carcinogenicity data for benz[a]-pyrene and dibenz[a,h]anthracene.

B. Aquatic

There are no standards or guidelines concerning allowable concentrations of IP in aquatic environments.

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No. 120

Isobutyl Alcohol

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

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Isobutyl Alcohol

I. Introduction

Isobutyl alcohol (2-methyl-1-propanol, $C_4H_{10}O$; molecular weight 74.12) is a flammable, colorless, refractive liquid with an odor like of amyl alcohol, but weaker. Isobutyl alcohol is used in the manufacture of esters for fruit flavoring essences, and as a solvent in paint and varnish removers. This compound is soluble in approximately 20 parts water, and is miscible with alcohol and ether.

II. Exposure

No data were readily available.

III. Pharmacokinetics

A. Absorption

Isobutyl alcohol is absorbed through the intestinal tract and the lungs.

B. Distribution

No data were readily available.

C. Metabolism

Isobutyl alcohol is oxidized to isobutyraldehyde and isobutyric acid in the rabbit, with further metabolism proceeding to acetone and carbon dioxide. Some conjugation with glucuronic acid occurs in the rabbit and dog.

D. Elimination

Approximately 14% of isobutyl alcohol is excreted as urinary conjugates in the rabbit.

IV. Effects

A. Carcinogenicity

Rats receiving isobutyl alcohol, either orally or subcutaneously, one to two times a week for 495 to 643 days showed liver carcinomas and

sarcomas, spleen sarcomas and myeloid leukamia (Gibel, et al., Z. Exp. Chir. Chir. Forsch. 7: 235 (1974).

B. Teratogenicity

No data were readily available.

C. Other Reproductive Effects

No data were readily available.

D. Chronic Toxicity

Ingestion of one molar solution of isobutyl alcohol in water by rats for 4 months did not produce any inflammatory reaction of the liver. On ingestion of two molar solution for two months rats developed Mallory's alcoholic hyaline bodies in the liver, and were observed to have decreases in fat, glycogen, and RNA in the liver.

E. Other Relevent Information

Acute exposure to isobutyl alcohol causes narcotic effects, and irritation to the eyes and throat in humans exposed to 100 ppm for repeated 8 hour periods. Formation of facuoles in the superficial layers of the cornea, and loss of appetite and weight were reported among workers subjected, to an undetermined, but apparently high concentration of isobutyl alcohol and butyl acetate. The oral LD_{50} of isobutyl alcohol for rates if 2.46 g/kg (Smith et al., Arch. Ind. Hyg. Occup. Med. 10: 61, 1954).

V. Aquatic Toxicity

A. Acute Toxicity

The LC_{50} of isobutyl alcohol for 24-hour-old Daphnia magna is between 10-1000 mg/l.

VI. Existing Guidelines and Standards

OSHA - 100 ppm
NIOSH - None
ACGIH - 50 ppm

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No. 121

Lead

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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DISCLAIMER

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LEAD

SUMMARY

The hazards of human exposure to lead have been well-recognized for centuries. The hematopoietic system is the most sensitive target organ for lead in humans, although subtle neurobehavioral effects are suspected in children at similar levels of exposure. The more serious health effects of chronic lead exposure, however, involve neurological damage, irreversible renal damage, and adverse reproductive effects observed only at higher levels of lead exposures. Although certain inorganic lead compounds are carcinogenic to some species of experimental animals, a clear association between lead exposure and cancer development has not been shown in human populations.

The effects of lead on aquatic organisms have been extensively studied, particularly in freshwater species. As with other heavy metals, the toxicity is strongly dependent on the water hardness. Unadjusted 96-hour LC_{50} values with the common fathead minnow, Pimephales promelas, ranged from 2,400-7,480 µg/l in soft water to 487,000 µg/l in hard water. Toxicity is also dependent on the life stage of the organism being tested. Chronic values ranged from 32 µg/l to 87 µg/l for six species of freshwater fish. Lead at 500 µg/l can reduce the rate of photosynthesis by 50 percent in freshwater algae. Lead is bioconcentrated by all species tested - both marine and freshwater - including

fish, invertebrates, and algae. The mussel, Mytilus edulis, concentrated lead 2,568 times that found in ambient water. Two species of algae concentrated lead 900-1000-fold.

LEAD

I. INTRODUCTION

This hazard profile is based primarily upon the Ambient Water Quality Criteria Document for Lead (U.S. EPA, 1979). A number of excellent comprehensive reviews on the health hazards of lead have also been recently published. These include the U.S. EPA Ambient Air Quality Criteria Document for Lead and the lead criteria document of the National Institute for Occupational Safety and Health (1978).

Lead (Pb, At. No. 82) is a soft gray acid-soluble metal used in electroplating, metallurgy, and the manufacture of construction materials, radiation protection devices, plastics, electronics equipment, storage batteries, gasoline antiknock additives, and pigments (NIOSH, 1978). The solubility of lead compounds in water depends heavily on pH and ranges from about 10^6 µg/l at pH 5.5 to 1 µg/l at pH 9.0 (U.S. EPA, 1979). Inorganic lead compounds are most stable in the +2 valence state, while organolead compounds are more stable in the +4 valence state (Standen, 1967).

Lead comsumption in the United States has been fairly stable from year to year at about 1.3×10^6 metric tons annually. Consumption of lead as an antiknock additive to gasoline (20 percent annual production) is expected to decrease steadily. Since lead is an element, it will remain indefinitely once released to the environment (U.S. EPA, 1979).

II. EXPOSURE

A. Water

Lead is ubiquitous in nature, being a natural constituent of the earth's crust. Most natural groundwaters have concentrations ranging from 1 to 10 µg/l.

Lead does not move readily through stream beds because it easily forms insoluble lead sulfate and carbonate. Moreover, it binds tightly to organic ligands of the dead and living flora and fauna of stream beds. However, lead has been found at high concentrations in drinking water (i.e., as high as 1000 µg/l), due primarily to conditions of water softness, storage, and transport (Beattie, et al. 1972).

The magnitude of the problem of excessive lead in drinking water is not adequately known. In one recent survey of 969 water systems, 1.4 percent of all tap water samples exceeded the 50 µg/l standard (McCabe, 1970). The U.S. EPA (1979) has not estimated a bioconcentration factor for lead in aquatic organisms.

B. Food

It is generally believed that food constitutes the major source of lead absorption in humans. The daily dietary intake of lead has been estimated by numerous investigators, and the results are generally consistent with one another. This dietary intake is approximately 241 µg/day for adults (Nordman, 1975; Kehoe, 1961). For children (ages 3 months to 8.5 years) the dietary intake is 40 to 210 µg of lead per day (Alexander, et al. 1973).

C. Inhalation

A great deal of controversy has been generated regarding the contribution of air to total daily lead absorption. Unlike the situation with food and water, ambient air lead concentrations vary greatly. In metropolitan areas, average air lead concentrations of 2 $\mu g/m^3$, with excursions of 10 $\mu g/m^3$ in areas of heavy traffic or industrial point sources, are not uncommon (U.S. EPA, 1979). In non-urban areas average air lead concentrations are usually on the order of 0.1 $\mu g/m^3$ (U.S. EPA, 1979).

III. PHARMACOKINETICS

A. Absorption

The classic studies of Kehoe (1961) on lead metabolism in man indicate that on the average and with considerable day-to-day excursions, approximately eight percent of the normal dietary lead (including beverages) is absorbed. More recent studies have confirmed this conclusion (Rabinowitz, et al. 1974). The gastrointestinal absorption of lead is considerably greater in children than in adults (Alexander, et al. 1973; Ziegler, et al. 1978).

It has not been possible to accurately estimate the extent of absorption of inhaled lead aerosols. To varying degrees, depending on their solubility and particle size, lead aerosols will be absorbed across the respiratory epithelium or cleared from the lung by mucociliary action and subsequently swallowed.

Very few studies concerning dermal absorption of lead in man or experimental animals are available. A

recent study by Rastogi and Clausen (1976) indicates that lead is absorbed through intact skin when applied at high concentrations in the form of lead acetate or naphthenate.

B. Distribution

The general features of lead distribution in the body are well known, both from animal studies and from human autopsy data. Under circumstances of long-term exposure, approximately 95 percent of the total amount of lead in the body (body burden) is localized in the skeleton after attainment of maturity (U.S. EPA, 1979). By contrast, in children only 72 percent is in bone (Barry, 1975). The amount in bone increases with age but the amount in soft tissues, including blood, attains a steady state early in adulthood (Barry, 1975; Horiuchi and Takada, 1954).

The distribution of lead at the organ and cellular level has been studied extensively. In blood, lead is primarily localized in the erythrocytes (U.S. EPA, 1979). The ratio of the concentration of lead in the cell to lead in the plasma is approximately 16:1. Lead crosses the placenta readily, and its concentration in the blood of the newborn is quite similar to maternal blood concentration.

C. Excretion

There are wide interspecies differences concerning routes of excretion for lead. In most species biliary excretion predominates in comparison to urinary excretion, except in the baboon (Eisenbud and Wrenn, 1970). It also appears that urinary excretion predominates in man (Rabino-

witz, et al. 1973). This conclusion, however, is based on very limited data.

IV. EFFECTS

A. Carcinogenicity

At least three studies have been published which report dose-response data for lead-induced malignancies in experimental animals (Roe, et al. 1965; Van Esch, et al. 1962; Zollinger, 1953; Azar, et al. 1973). These studies established that lead caused renal tumors in rats.

Several epidemiologic studies have been conducted on persons occupationally exposed to lead (Dingwall-Fordyce and Lane, 1963; Nelson, et al. 1973; Cooper and Gaffey, 1975; Cooper, 1978). These reports do not provide a consistent relationship between lead exposure and cancer development.

B. Mutagenicity

Pertinent information could not be located in the available literature concerning mutagenicity of lead. However, there have been conflicting reports concerning the occurrence of chromosomal aberrations in lymphocytes of lead-exposed workers (O'Riordan and Evans, 1974; Forni, et al. 1976).

C. Teratogenicity

In human populations exposed to high concentrations of lead, there is evidence of embryotoxic effects although no reports of teratogenesis have been published (U.S. EPA, 1979). In experimental animals, on the other hand, lead has repeatedly produced teratogenic effects (Cat-

zione and Gray, 1941; Karnofsky and Ridgway, 1952; McClain and Becker, 1975; Carpenter and Ferm, 1977; Kimmel, et al. 1976). Positive results were shown by injection into the yolk sac of chick embryos and by intravenous and intraperitoneal injection in rats and hamsters. Chronic administration of lead in the drinking water of pregnant rats at concentrations up to 250 µg/l resulted in delayed fetal development and fetal resorption without teratologic effects (Kimmel, et al. 1976).

D. Other Reproductive Effects

Lead has caused miscarriages and stillbirths among women working in the lead trades (Lane, 1949; Nogaki, 1958). In addition, decreased sperm quality in lead-exposed human males (Lancranjan, et al. 1975) and reduced fertility in animals of both sexes (Stowe and Goyer, 1971; Jacquet, et al. 1975) have been reported.

E. Other Chronic Toxicity

There is considerable information in man concerning the renal effects of lead in both adults and children (Clarkson and Kench, 1956; Chisolm, 1968; Cramer, et al. 1974; Wedeen, et al. 1975). Two distinctive effects on the kidney occur with lead absorption. One is reversible proximal tubular damage, which is seen mainly with short-term exposure. The other effect is reduced glomerular filtration, which has generally been considered to be of a slow, progressive nature. Human exposures to high concentrations of lead have also been associated with cerebrovascular disease (Dingwall-Fordyce and Lane, 1963), heart failure

(Kline, 1960), electrocardiographic abnormalities (Kosmider and Pentelenz, 1962), impaired liver function (Dodic, et al. 1971), impaired thyroid function (Sandstead, et al. 1969), and intestinal colic (Beritic, 1971).

V. AQUATIC TOXICITY

A. Acute Toxicity

The available data base on the toxic effects of lead to freshwater organisms is quite large and clearly demonstrates the relative sensitivity of freshwater organisms to lead. The data base shows that the different lead salts have similar LC_{50} values, and that LC_{50} values for lead are greatly different in hard and soft water. Between soft and hard water, the LC_{50} values varied by a factor of 433 times for rainbow trout, 64 times for fathead minnows, and 19 times for bluegills (Davies, et al. 1976; Pickering and Henderson, 1966).

Some 96-hour LC_{50} values for freshwater fish are 2,400 to 7,480 µg/l for fathead minnows in soft water (Tarzwell and Henderson, 1960; Pickering and Henderson, 1966), 482,000 for fathead minnows in hard water (Pickering and Henderson, 1966), 23,800 µg/l for bluegills in soft water (Pickering and Henderson, 1966), and 442,000 µg/l for bluegills in hard water (Pickering and Henderson, 1966).

For invertebrate species, Whitely (1968) reported 24-hour LC_{50} values of 49,000 and 27,500 µg/l for sludge worms (Tubifex sp.) obtained from tests conducted at pH

levels of 6.5 and 8.5, respectively. The effects of water hardness on toxicity of lead to invertebrates could not be located in the available literature.

The acute toxicity data base for saltwater organisms is limited to static tests with invertebrate species. The LC_{50} values ranged from 2,200 to 3,600 µg/l for oyster larvae in a 48-hour test (Calabrese, et al. 1973) to 27,000 µg/l for adult soft shell clams (Eisler, 1977) in a 96-hour test.

B. Chronic Toxicity

Chronic tests in soft water have been conducted with lead on six species of fish. The chronic values ranged from 32 µg/l for lake trout (Sauter, et al. 1976) to 87 µg/l for the white sucker (Sauter, et al. 1976), both being embryo-larval tests.

Only one invertebrate chronic test result was found in the literature. This test was with Daphnia magna in soft water, and the resulting chronic value was 55 µg/l, about one-eighth the acute value of 450 µg/l (Biesinger and Christensen, 1972).

Life cycle or embryo-larval tests conducted with lead on saltwater organisms could not be located in the available literature.

C. Plant Effects

Fifteen tests on eight different species of aquatic algae are found in the literature. Most studies measured the lead concentration which reduced $^{14}CO_2$ fixation by 50 percent. These values range from 500 µg/l for Chlorella

sp. (Monahan, 1976) to 28,000 for a diatom, Navicula (Malanchuk and Gruendling, 1973).

Pertinent data could not be located in the available literature on the effects of lead on marine algae.

D. Residue

The mayfly (Ephemerella grandis) and the stonefly (Pteronarcys californica) have been studied for their ability to bioconcentrate lead (Nehring, 1976). The bioconcentration factor for lead in the mayfly is 2,366 and in the stonefly 86, both after 14 days of exposure.

Schulz-Baldes (1972) reported that mussels (Mytilus edulis) could bioconcentrate lead 2,568-fold. Two species of algae bioconcentrate lead 933 and 1,050-fold (Schulz-Baldes, 1976).

VI EXISTING GUIDELINES AND STANDARDS

A. Human

As of February 1979, the U.S. Occupational Safety and Health Administration has set the permissible occupational exposure limit for lead and inorganic lead compounds at 0.05 mg/m^3 of air as an 8-hour time-weighted average. The U.S. EPA (1979) has also established an ambient airborne lead standard of 1.5 $\mu g/m^3$.

The U.S. EPA (1979) has derived a draft criterion for lead of 50 µg/l for ambient water. This draft criterion is based on empirical observation of blood lead in human population groups consuming their normal amount of food and water daily.

B. Aquatic

For lead, the draft criterion to protect freshwater aquatic life is:

$$e^{(1.51 \ln (\text{hardness}) - 3.37}$$

as a 24-hour average, where e is the natural logarithm; the concentration should not exceed:

$$e^{(1.51 \ln (\text{hardness}) - 1.39)}$$

at any time (U.S. EPA, 1979).

For saltwater aquatic life, no draft criterion for lead was derived.

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No. 122

Maleic Anhydride

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

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MALEIC ANHYDRIDE

SUMMARY

Maleic anhydride is readily soluble in water where it hydrolyzes to form maleic acid. It is readily biodegraded by microorganisms and is not expected to bioconcentrate.

Maleic anhydride induced local tumors in rats following repeated subcutaneous injections. Maleic anhydride is an acute irritant and can be an allergen in sensitive individuals.

I. INTRODUCTION

A. Chemical Characteristics

Maleic anhydride ($C_4H_2O_3$; 2,5-furandione; CAS No. 108-31-6) is a white, crystalline solid with an acrid odor. The chemical has the following physical/chemical properties (Windholz, 1976):

Molecular Weight:	98.06
Boiling Point:	202.0°C
Melting Point:	52.80°C
Solubility:	Soluble in water and many organic solvents

A review of the production range (includes importation) statistics for maleic anhydride (CAS No. 108-31-6) which is listed in the initial TSCA Inventory (1979a) has shown that

between 200 million and 300 million pounds of this chemical were produced/imported in 1977. */

Maleic anhydride is used as a chemical intermediate in the production of unsaturated polyester resins, fumaric acid, pesticides, and alkyd resins (Hawley, 1977).

II. EXPOSURE

A. Environmental Fate

Maleic anhydride is readily soluble in water where it hydrolyzes to form maleic acid (Hawley, 1977; Windholz, 1976). Matsui et al. (1975) reported that maleic anhydride in wastewater is easily biodegraded by activated sludge.

B. Bioconcentration

Maleic anhydride is not expected to bioaccumulate (U.S. EPA, 1979b).

C. Environmental Occurrence

The major source of maleic anhydride emissions is associated with release of the chemical as a byproduct of phthalic anhydride manufacture. Emissions can also occur during the production and handling of maleic anhydride and its derivatives (U.S. EPA, 1976).

*/This production range information does not include any production/importation data claimed as confidential by the person(s) reporting for the TSCA Inventory, nor does it include any information which would compromise Confidential Business Information. The data submitted for the TSCA Inventory, including production range information, are subject to the limitations contained in the Inventory Reporting Regulations (40 CFR 710).

III. PHARMACOKINETICS

No data were found. Nonetheless, it is expected that any maleic anhydride that is absorbed would be hydrolyzed to maleic acid and then neutralized to a maleate salt. Maleate should be readily metabolized to CO_2 and H_2O.

IV. HEALTH EFFECTS

A. Carcinogenicity

Dickens (1963) reported that local fibrosarcomas developed in rats after repeated subcutaneous injections of maleic anhydride suspended in arachis oil. Multiple injections of arachis oil alone or a hydrolysis product derived from maleic anhydride (sodium maleate) did not produce any tumors at the injection site.

A long term dietary study of maleic anhydride in rats for possible carcinogenicity is now in progress. Terminal necropsies are schedules for January, 1980 (CIIT, 1979).

B. Other Toxicity

Maleic anhydride vapors and dusts are acute irritants of the eyes, skin, and upper respiratory tract (ACGIH, 1971). Repeated exposures to maleic anhydride concentrations above 1.25 ppm in air have caused asthmatic responses in workers. Allergies have developed in which workers have become sensitive to even lower concentrations of the compound. An increased incidence of bronchitis and dermatitis has also been noted among workers with long-term exposure to maleic anhydride. One case of pulmonary edema in a worker has been reported (U.S. EPA, 1976).

V. AQUATIC EFFECTS

The 24 to 96-hr median threshold limit (TLm) for maleic anhydride in mosquito fish is 230-240 mg/l. The 24-hr TLm for bluegill sunfish is 150 mg/l (Verschueren, 1977).

VI. EXISTING GUIDELINES

The existing OSHA standard for maleic anydride is an 8-hour time weighted average (TWA) of 0.25 ppm in air (39CFR23540).

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No. 123

Malononitrile

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

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DISCLAIMER

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MALONONITRILE

Summary

Nitriles, as a group, are sources of the cyanide ion, which interferes with basic cellular oxidative mechanisms. Malononitrile has effects on the cardiovascular, renal, hepatic and central nervous systems. This compound can take effect after inhalation, dermal contact or ingestion. No carcinogenic, mutagenic or teratogenic effects have been reported.

Malononitrile has been used in the treatment of various forms of mental illness. A thorough documentation of the side effects of this compound exists. The only human toxicity data on malononitrile found in the available literature are those reported during clinical psychiatric use.

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MALONONITRILE

I. INTRODUCTION

Malononitrile ($NCCH_2CH$), CAS registry number 109-77-3, is an odorless, yellow crystalline chemical with a molecular weight of 66.06 and a specific gravity of 1.049. Its melting point is between 30°C and 31°C. Malononitrile is soluble in water, acetone, alcohol and ether, but is insoluble in ethanol (Weast, 1974). When heated to decomposition, nitriles emit toxic fumes containing cyanides (Sax, 1968).

Malononitrile is used in the following applications: as a lubricating oil additive, for thiamine synthesis, for pteridine-type anti-cancer agent synthesis, and in the synthesis of photosensitizers, acrylic fibres, and dyestuffs (Eur. Chem. News, 1975; Lonza Inc., 1978).

Imports of malononitrile, which currently is not manufactured in the United States, were 60,000 pounds for 1976 (NIOSH, 1978).

II. EXPOSURE

A. Water and Food

Pertinent data were not found in the available literature.

B. Inhalation

Research by Panov (1969) indicates that malononitrile was readily absorbed by the lungs of animals. As test chamber temperatures increased, the mortality rate also increased, presumably due to higher absorption.

The major occupational exposure to nitriles occurs principally by inhalation of vapor or aerosols and by skin absorption. The likelihood of such exposure increases during the handling, transferring and quality control sampling of these compounds.

C. Dermal

Panov (1969) reported that malononitrile was readily absorbed through the eyes of rabbits. He also reported that mice and rabbits absorb the compound through the skin. Extreme irritation resulted from both modes of application.

III. PHARMACOKINETICS

A. Absorption

Animal studies indicated that malononitrile is absorbed through the lungs and by the skin (Panov, 1969).

B. Distribution

Hicks (1950) determined that, to some extent, malononitrile exerts tissue specificity (brain, liver, kidney, lung and thyroid) in its action.

The formation of thiocyanate *in vitro* from malononitrile and thiosulfate was highest in the presence of liver tissue, lowest with brain, and intermediate with kidney (Stern et al., 1952).

C. Metabolism

The dinitrile compounds (such as malononitrile) presumably can exert a greater toxic effect than the mononitriles due to the more rapid release of cyanide from the parent compound. Malononitrile released cyanide *in vivo* and was ultimately excreted as thiocyanate after oxidation (Ghiringhelli, 1955).

The C≡N group may be converted to a carboxylic acid derivative and ammonia, or may be incorporated into cyanocobalamine. Ionic cyanide also reacts with carboxyl groups and with disulfides (McKee et al., 1962).

Stern et al. (1952) found that *in vitro* respiration of brain, kidney, and liver slices was inhibited by 0.01 M malononitrile. The same investigators also demonstrated the formation of thiocyanate from malononitrile and thiosulfate in liver and kidney tissues *in vitro*. The release of cyanide from dinitriles suggests that their mechanism of acute toxicity may be similar to that of the mononitriles.

The enzyme rhodanase, which catalyzed the formation of thiocyanate from cyanide and thiosulfate, was ineffective in the catalysis of thiocyanate from malononitrile. *In vivo* thiocyanate formation apparently came from an intermediate metabolite and not the malononitrile molecule.

D. Excretion

After absorption, malononitrile may be metaboilized to an organic cyanide, which is oxidized to thiocyanate and excreted in the urine (McKee et al, 1962). No evidence of respiratory excretion was found in the available literature.

IV. EFFECTS

A. Carcinogenicity, Mutagenicity, Teratogenicity and Reproductive Effects

Pertinent data were not found in the available literature.

B. Chronic Toxicity

The only available human toxicity data on malononitrile are those reported during the clinical use of the compound in the treatment of mental illness.

Hyden and Hartelius (1948) reported on the clinical use of malononitrile during psychiatric treatment. Its intended purpose was to stimulate the production of proteins and nucleic acids in the pyramidal cells of the frontal cortices of psychiatric patients, particularly those who were depressed or schizophrenic. All patients experienced tachycardia 10 to 20

minutes after the infusion of malononitrile (1-6 mg/kg). Facial redness, headache, nausea, vomiting, shivering, cold hands and feet, muscle spasms and numbness were also reported with varying frequency. Similar results were also submitted by MacKinnon et al. (1949), Hartelius (1950), and Meyers et al. (1950) in the treatment of mental patients.

Hicks (1950) reported that malononitrile poisoning induced brain lesions in rats. The compound produced demyelinating lesions of the optic tract and nerve, the cerebral cortex, the olfactory bulb and the substantia nigra.

Panov (1969) found the repeated exposure to malononitrile (36 mg/m^3 for 2 hours per day for 35 days) was slightly toxic to rats. The exposure caused slight anaplasia of bone-marrow, i.e. a lower hemoglobin level and elevated reticulocyte count.

F. Acute Toxicity

Panov (1969) subjected mice to a single, 2-hour inhalation exposure to malononitrile. The mice showed signs of restlessness and increased respiration rate in the early post-treatment period followed by Lassitude, decreased respiration rate, cyanosis, noncoordination of movement, trembling, convulsions and eventual death of some animals. The exposure concentration was not noted.

Panov (1969) reported that liquified malononitrile applied to the eyes of rabbits caused tearing, blepharospasm. hyperemia of the conjunctiva, and swelling of the eyelids. Panov also applied malononitrile solution (concentration not stated) to the tails of mice. The animals showed signs of restlessness, rapid respiration and slight cyanosis of the extremities and the mucosa of the lips. He also observed trembling and skin irritation following dermal application of malononitrile to a rabbit.

Nuclear changes in neurons and satellite spiral ganglia were seen in rats administered single doses (6-8 mg/kg) of malononitrile (Van Breeman and Hiraoka, 1961).

V. AQUATIC TOXICITY

Pertinent data were not found in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

Because malononitrile is about three times as toxic as isobutyronitrile, NIOSH recommends that employee exposure to malononitrile not exceed 3 ppm (8 mg/m^3) as a TWA limit for up to 10-hour workshift in a 40-hour work week (NIOSH, 1978).

B. Aquatic

Pertinent data were not found in the available literature.

MALONONITRILE

References

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No. 124

Mercury

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

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MERCURY

SUMMARY

Short chain alkyl mercurials represent a toxic species that distributes widely and accumulates in the liver, kidneys and other organs. These compounds are eliminated from the body at a slow rate. In humans, mercurials have been associated with neurological disorders, sensory impairment and tremors. Prenatal exposure has produced psychomotor disorders.. Brain development is impaired by accumulation of mercurials, and lesions in the cerebral and cerebellar areas have been observed.

Methylmercury crosses the placental barrier and is secreted in milk. Methylmercury and mercuric chloride have been shown to produce teratogenic effects in animals. Reproductive effects in animals of alkyl mercury compounds involve reversible inhibition of spermatogonia and damage to unfertilized gametes. A high infant mortality rate has been reported in a study of mothers exposed to high levels of mercurials.

Mercurials have induced chromosome breakage in plant cells and point mutations in Drosophila. Mercurials have not been shown to produce carcinogenic effects other than non-specific injection site sarcomas. The U.S. EPA (1979) has calculated an Acceptable Daily Intake (ADI) for mercury of 200 µg/day.

Mercury can be bioconcentrated many-fold in fish and other aquatic organisms because of rapid uptake and the excretion of

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mercury from their tissues. In general, the methylmercury compounds are more toxic than the inorganic forms of mercury. Toxicity varies widely among species. Concentrations as low as 0.1 µg/l have been shown to be toxic to freshwater crayfish.

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MERCURY

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Mercury (U.S. EPA, 1979).

Mercury (Hg; atomic weight 200.59) is a silver-white metal, which is a liquid at room temperature. It has the following physical properties: melting point, -38.87°C; boiling point, 356-358°C; specific gravity, 13.546; and vapor pressure at 20°C, 0.0012 mm Hg (Stecher, 1968).

Mercury exists in three oxidation states: elemental (0), mercurous (+1), and mercuric (+2). The solubilities of some common mercuric salts are as follows: $HgCl_2$ (1 g/13.5 ml water), $Hg(NO_3)_2$ (soluble in a "small amount" of water), $Hg(CH_3COO)_2$ (1 g/2.5 ml water) (Stecher, 1968). Mercurous salts are much less soluble in water; Hg_2Cl_2 is practically insoluble in water (Stecher, 1968).

Major usage of mercury include the following: as a cathode in the electrolytic preparation of chlorine and caustic soda, in electrical apparatus, in industrial and control instruments, in general laboratory applications, in dental amalgams, in anti-fouling and mildew-proofing paints, and as a fungicide in treating seeds, bulbs, and plants. However, mercury is no longer registered by the U.S. EPA for this last application.

Elemental mercury can be oxidized to the mercuric form in water in the presence of oxygen (Stock and Cucuel, 1934); this transformation in water is facilitated by the presence of organic substances (Jensen and Jernelov, 1972). The mercuric

ion is a substrate for biomethylation reactions; both dimethyl and monomethyl mercury may be formed by bacteria present in sediments (Wood, 1976 and Cotton and Wilkinson, 1966). Considerable bacterial demethylation of methylmercury occurs in the environment, limiting the buildup of methylmercury (Tonomura and Konzaki, 1969). The degree of oxygenation, pH, and the presence of inorganic and organic ligands are determining factors regulating which state of mercury is present in water. On thermodynamic grounds, one would expect inorganic mercury to be present mainly as mercuric compounds in well-oxygenated water and, in an increasing fraction of total mercury, as the elemental form or the sulfide form under reducing conditions (NAS, 1978).

II. EXPOSURE

Mercury undergoes a global cycle of emission and deposition. Total entry of mercury into the atmosphere is approximately 40,000 to 50,000 metric tons per year, mainly from natural sources (NAS, 1978 and Korringa and Hagel, 1974). Deposition from the atmosphere into the ocean is estimated at about 11,000 tons per year (NAS, 1978). These waters represent a relatively large mercury pool that maintains a stable concentration (U.S. EPA, 1979).

Industrial release of mercury involves both organic and inorganic forms. These emissions are from the burning of fossil fuels, discharges of waste from the chloralkali industries, discharges of methylmercury from chemical manufacturers, and runoff from the use of ethyl and methylmercury fungicides (U.S. EPA, 1979).

Based on available monitoring data, the U.S. EPA (1979) has estimated the uptake of mercury by adult humans from air, water, and food:

Source	Adult - µg/day Minimum	Maximum	Predominant form
Air	0.3	0.8	elemental
Water	0.1	0.4	mercuric
Food	3.0	5.0	methylmercury
Total	3.4	6.2	

Fish and shellfish represent a source of high methylmercury intake. The U.S. EPA (1979) has estimated average bioconcentration factors of 1,700 for mercuric chloride and 6,200 for methylmercury in the edible portions of fish and shellfish consumed by Americans. This estimate is based on bioconcentration studies in several species, and on other factors.

III. PHARMACOKINETICS

A. Absorption

Inorganic mercury salts are absorbed poorly by the human gastrointestinal tract; less than 15 percent absorption was reported (Rahola, et al., 1971). Inhalation of mercuric oxide has been shown to produce pulmonary deposition and absorption of the compound, with 45 percent of the administered dose cleared within 24 hours (Morrow, et al., 1964). Dermal absorption of mercuric chloride has been reported in studies with guinea pigs (Friberg, et al., 1961; Skog and Vahlberg, 1964).

Metallic mercury is not absorbed significantly from the gastrointestinal tract. Friberg and Nordberg (1973) calculate that less than 0.01 percent of an orally administered dose is absorbed. Studies with human subjects reveal approximately 80

percent of inhaled mercury vapor is retained (Hursh, et al., 1976), with alveolar regions indicated as the probable site of absorption into the bloodstream (Berlin, et al., 1969). Animal studies indicate dermal absorption of metallic mercury can occur (Juliusberg, 1901; Schamberg, et al., 1918).

Methylmercury shows virtually complete absorption from the gastrointestinal tract (Aberg, et al., 1969; Miettinen, 1973). Inhalation of alkyl mercurials leads to high retention, perhaps as high as 80 percent (Task Group on Metal Accumulation, 1973). Severe poisoning of humans following topical methylmercury applications indicates some dermal absorption of the compound (U.S. EPA, 1979).

B. Distribution

Methylmercury, after absorption from the gastrointestinal tract, distributes readily to all tissues in the body (WHO Expert Committee, 1976), with the highest concentrations being found in the kidney cortex and red blood cells. Approximately five percent of an ingested dose is found in the blood compartment following tissue distribution. Human studies with a radioactively labeled compound have indicated that approximately ten percent of the body burden may be transferred to the head region following complete tissue distribution (Aberg, et al., 1969). The ratio of methylmercury in the brain to levels in the blood may be as high as 10:1 (U.S. EPA, 1979). In muscle tissue, analysis of the mercury present indicates that it is almost entirely methylmercury, while liver and kidney contain a substantial amount of demethylated, inorganic forms (Magos, et al., 1976).

Determination of methylmercury in cord blood and fetal red cells indicates that the compound is transported across placental membranes (Tejing, 1970; Suzuki, et al., 1971). Methylmercury is secreted in mother's milk and may average as much as five percent of the maternal blood level (Bakir, et al., 1973).

Mercury in the mercuric form concentrates in the kidneys following inhalation of mercury vapor. Animal studies show that up to 90 percent of an administered dose may localize at this site (Rothstein and Hayes, 1964). Experiments using radiolabeled mercury in human volunteers have shown approximately seven percent accumulation of the inhaled compound in the head region (Hursch, et al., 1976). Oxidation of absorbed elemental mercury to the mercuric form takes place in vivo, probably largely through the enzymatic activities of red blood cells (Clarkson, et al., 1978).

Mercury has been shown to be transferred into the fetus after maternal exposure. The rate of transfer of elemental mercury appears to be greater than ionic forms of mercury (Clarkson, et al., 1972).

Animal studies with inorganic mercury salts indicate the distribution pattern is similar to the pattern observed after exposure to mercury vapors (Friberg and Vostal, 1972); however, the ratio of mercuric ion in red cells to plasma levels is lower (Rahola, et al., 1971). The major site of mercuric ion accumulation is the kidney (U.S. EPA, 1979).

C. Metabolism

Methylmercury undergoes cleavage of the carbon mercury bond, resulting in the production of inorganic mercury in vivo.

Plasma, liver, and kidney all contain substantial amounts of inorganic mercury following administration of the organic form of the compound (Bakir, et al., 1973). Norseth and Clarkson (1971) have suggested that gut microflora may aid in this biotransformation. Bakir, et al. (1973) have determined a mean half-life value of 65 days for 16 hospital cases. However, a wide range of blood half-lives have been determined in human studies (U.S. EPA, 1979). Whole body half-life values for methylmercury appear to be in the same range (~52-93 days) as blood clearance half-lives (Miettinen, 1973).

Elemental mercury can undergo oxidation in the body to the mercuric form, which is then capable of interacting with many tissue ligands (Clarkson, et al., 1978). Limited experiments with subjects exposed to mercury vapor indicate a two component loss of mercury from the bloodstream. Clarkson (1978) has estimated half-lives of 2.4 days for the fast component and 14.9 days for the slow component following a brief exposure to mercury vapor. Hursh, et al. (1976) have estimated that the whole body half-life of elemental mercury is comparable with that of methyl mercury.

D. Excretion

The excretion of methylmercury occurs predominantly by the fecal route in humans. Less than ten percent of excretion occurs in the urine (U.S. EPA, 1979). Norseth and Clarkson (1971) have determined significant biliary secretion of methylmercury in animals, raising the possibility that biotransformation to the inorganic form might be affected by microflora in the gut.

Elemental mercury exposure has been shown to lead to mercury excretion predominantly through the feces and urine (Lovejoy, et al., 1974). As kidney levels of mercury increase, a greater urinary excretion of the compound occurs (Rothstein and Hayes, 1964). Urinary excretion values from 13 percent to 58 percent have been determined. Elimination of inhaled mercury has been observed in expired air (7 percent) (Cherian, et al., 1978) and in sweat (Lovejoy, et al., 1974).

Human studies with small ingested doses of mercuric salts have indicated that following excretion of the unabsorbed compound, urinary and fecal excretion of inorganic mercury were approximately equal (Rahola, et al., 1971).

IV. EFFECTS

A. Carcinogenicity

Intraperitoneal injection of metallic mercury into rats produced injection site sarcomas (Druckrey, et al., 1957).

Pertinent data could not be located in the available literature indicating that mercury is carcinogenic.

B. Mutagenicity

Methylmercury has been shown to block mitosis in plant cells and in human leukocytes treated in vivo, and human cells in vitro, as well as to induce chromosome breakage in plant cells and point mutations in Drosophila (Swedish Expert Group, 1971; Ramel, 1972).

No evidence for the mutagenic effects of elemental or inorganic mercury could be located in the available literature.

C. Teratogenicity

Oharazawa (1968) reported increased frequency of cleft palate in mice treated with an alkyl mercury compound. Embryotoxic effects without gross teratological effects were reported by Fujita (1969) in mice. Prenatal exposure to methylmercury has produced histological evidence of brain damage in several species (Matsumoto, et al., 1967; Nonaka, 1969; Morikawa, 1961). Spyker and Smithburg (1972) and Olson and Massaro (1977) have also reported anatomical malformations in animals exposed prenatally to methylmercury.

Teratological effects of mercuric chloride have been reported in animals (Gale and Ferm, 1971). However, data are not available on the teratogenicity of inorganic mercury in human populations.

Exposure of rats prenatally to mercury vapor produced fetal toxicity without evidence of teratological effects (Baranski and Szymczyk, 1973).

D. Other Reproductive Effects

A high mortality rate in infants born to women suffering mercury poisoning has been reported (Baranski and Szymczyk, 1973).

Methylmercury has been reported to interfere with reproductive capability in adult animals treated with this compound (Ramel, 1972; Suter, 1975). Khera (1973) has observed that administration of alkyl mercury compounds to rats may damage gametes prior to fertilization. Reversible inhibition of spermatogonial cells in mice treated with mercuric chloride has been reported (Lee and Dixon, 1975).

E. Chronic Toxicity

Chronic exposure to methylmercury has produced several outbreaks of poisoning, characterized by neurological symptoms following central nervous system damage (Nordberg, 1976; NAS, 1978). Adult exposure to methylmercury has produced symptoms of paresthesia of the extremities, impaired peripheral vision, slurred speech, and unsteadiness of gait and of limbs (U.S. EPA, 1979). Neuropathological investigation showed cerebellar atrophy and focal atrophy of the calcarine cortex (Hunter and Russell, 1954).

Prenatal exposure to methylmercury produced psychomotor brain abnormalities (Engleson and Herner, 1952; Harada, 1968). Brain development was shown to be disturbed, and both cerebral and cerebellar lesions were observed (U.S. EPA, 1979). An epidemiological study on school children in the Minamata Bay area has reported a higher incidence of neurological deficits, learning difficulties, neurological symptoms, and poor performance on intelligence tests for these residents of a high methylmercury exposure region (Med. Tribune, 1978).

An ethylmercury poisoning outbreak indicated renal and cardiac damage following this exposure (Jalili and Abbasi, 1961).

Mercury vapor poisoning may produce signs of mental disturbances, tremors, and gingivitis (U.S. EPA, 1979). Exposure to extremely high concentrations can damage lung tissue causing acute mercurial pneumonitis. Kidney dysfunction (proteinuria) in workers exposed to mercury vapor has also been reported (Kazantzis, et al., 1962; Joselow and Goldwater, 1967).

V. AQUATIC TOXICITY

A. Acute Toxicity

Observed LC_{50} values for three flow-through and two static-renewal assays for mercuric chloride with the rainbow trout as the test species ranged from 155 to 903 µg/l. The results of two flow-through and three static-renewal assays on rainbow and brook trout provide an LC_{50} range for methylmercuric compounds from 24 to 84 µg/l, with the rainbow trout being from three to five times as sensitive as the brook trout. For five other mercury compounds, LC_{50} values ranged from 5.1 for phenylmercuric acetate to 39,910 µg/l for merthiolate. Ethyl- and phenylmercury compounds generally were more toxic while merthiolate and pyridylmercuric acetate were less toxic. A total of 14 freshwater invertebrate species have been tested in static and static-renewal bioassays for acute toxicity to mercuric chloride and mercuric nitrate. LC_{50} values ranged from 0.02 to 2,100 µg/l (U.S. EPA, 1979). Heit and Fingerman (1977) and Beisinger and Christensen (1972) reported the more sensitive species to be the crayfish Faxonella clypeata and the daphnid, Daphnia magna, respectively. Warnick and Bell (1969) reported that the mayfly (Ephemerella subvaria), the stonefly (Acroneuria lycorius), and the caddisfly (Hydropsyche betteni) were among the most resistant freshwater invertebrates to mercuric chloride. Two static tests have produced 96-hour LC_{50} values of 800 and 2,000 µg/l for mercuric chloride to the marine fish, the mummichog (Fundulus heteroclitus). Among marine invertebrates exposed to mercuric chloride, LC_{50} values ranged from 3.6 to 32,000 µg/l for 21 species. Embryo

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stages of the oyster (Crassostrea virginica), the hard-shell clam (Mercenaria mercenaria), and the mysid shrimp (Mysidopsis bahia), the latter in the only acute flow-through test reported, were the more sensitive species reported. Lockwood and Inman (1975) provide the only acute study for methylmercuric chloride with a adjusted 96-hour LC_{50} value of 150 µg/l.

B. Chronic Toxicity

McKim, et al. (1976) offered the single source reported for chronic effects to freshwater fish. Examining the long-term effects of methylmercury chloride on three generations of the brook trout (Salvelinus fontinalis), adverse effects were reported at 0.93 µg/l, but not at 0.29 µg/l. Brook trout were from three to four times more resistant than rainbow trout (Salmo gairderi). Sosnowski, et al. (1979) have examined the effects of mercuric chloride by a flow-through, life-cycle bioassay on the mysid shrimp, Mysidopsis bahia. The highest concentration producing no-observed-effect was 0.82 µg/l.

C. Plant Effects

A number of different parameters have been used to determine the toxic effects of mercury compounds on freshwater plants. Effective concentrations of mercuric chloride ranged from 60 to 2,590 µg/l. Blinn, et al. (1977) demonstrated altered photosynthetic activity in a summer assemblage of algal species at 60 µg/l. Two of these studies on the effects of methylmercury chloride to freshwater algae revealed enzyme inhibition at 1,598 µg/l in Anklstrodesmus braunii and 50 percent growth inhibition to Coelastrum microporum at concentrations of 2.4 to 4.8 µg/l. For other organomercury compounds, effective concentrations ranged

from less than 0.6 to 200.6 µg/l. Using 18 marine species, Berland, et al. (1976) measured growth inhibition at mercuric chloride concentrations from 5 to 15 µg/l and lethalities from 10 to 50 µg/l. Effective concentrations for the alga Isochrysis galbana ranged up to 2,000,000 µg/l, at which no growth was observed (Davies, 1976). For other organomercury compounds, effective concentrations ranged from 0.1 to less than 2,000 µg/l. Harriss, et al. (1970) reported reduced photosynthetic activity to methylmercury hexachlorophthalimine in the diatom, Nitzchia delictissima, at the level of 0.1 µg/l. Methylmercury chloride was reported by Overnell (1975) to reduce photosynthetic activity at concentrations of less than 2,000 µg/l.

D. Residues

Bioconcentration data for freshwater species for various mercury compounds can be summarized by the following bioconcentration factors: 33,800 for the algae Synedra ulna (Fujita and Hashizuma, 1972) exposed to mercuric chloride; 4,532 to 8,049 for juvenile rainbow trout exposed to methylmercury chloride (Reinert, et al., 1974); 12,000 to 20,000 for brook trout exposed to methylmercury chloride (McKin, et al., 1976); and 62,898 for the fathead minnow exposed to methylmercury chloride (Olson, et al., 1975). It should be noted that for the high bioconcentration value for the fathead minnow, the fish were allowed to forage on aquatic organisms growing within the mercury enriched exposure chambers; therefore, this measurement may more closely reflect actual field data. The trout were fed a pelleted diet. A variety of marine organisms have been used to demonstrate the rapid accumulation of inorganic and organic mercury compounds.

Bioconcentration values for marine algae ranged from 853 to 7,400, with exposure periods of two to eight days for mercuric chloride. A 30-day bioconcentration factor of 129 for the lobster, Homarus americanus, has been reported by Thurberg, et al. (1977), and a range of 2,800 to 10,000 reported for adult oysters, Crassostrea virginica, (both species for mercuric chloride). Kopfler (1974) reports a biomagnification value of 40,000 for the oyster C. virginica to methylmercury and phenyl-mercury chloride. The biological half-lives of rapidly accumulated mercuric compounds indicate that clearance is not rapid even after several months.

VI. EXISTING GUIDELINES

A. Human

The U.S. EPA has recommended a drinking water standard of 2 ug Hg/l to protect human health (U.S. EPA, 1973).

Calculation of an acceptable daily intake (ADI) of mercury by the U.S. EPA (1979) has produced a tentative criterion of 0.2 µg/l (with an uncertainty factor applied) for ambient water.

B. Aquatic

The criteria for mercury are divided into tentative recommendations for inorganic and organic mercury. Freshwater criteria have been drafted as follows: for inorganic mercury, the draft criterion is 0.064 µg/l for a 24-hour average exposure, not to exceed 3.2 µg/l at any time. For methylmercury, the draft criterion is 0.016 µg/l for a 24-hour average, not to exceed 8.8 µg/l at any time. To protect marine life from inorganic mercury, the draft criterion is 0.19 µg/l for a 24-hour average, not to exceed 1.0 µg/l at any time. For methylmercury, the tenta-

tive criterion is 0.025 µg/l as a 24-hour average not to exceed 2.6 µg/l at any time (U.S. EPA, 1979).

The above criteria have not yet gone through the process of public review; therefore, there is a possibility that the criteria may be changed.

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No. 125

Methomyl

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

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METHOMYL

Summary

Methomyl is a toxic carbamate insecticide used on field crops and fruit. It is readily absorbed through inhalation or dermal exposure and is almost completely eliminated from the body within 24 hours. Chronic toxicity studies in rats and dogs show that no effects occur below 100 ppm. The threshold limit value for methomyl in air is 2.5 $\mu g/m^3$. Methomyl inhibits the activity of cholinesterase in the body. Studies have shown that methomyl is not carcinogenic in rats and dogs or mutagenic in the Ames bioassay. However, a different type of bioassay showed mutagenic activity at a methomyl concentration of 50 ppm. A potential product of the reaction of methomyl with certain nitrogen compounds in the environment or in mammalian systems is nitrosomethomyl, which is a potent mutagen, carcinogen, and teratogen.

Methomyl is toxic to many aquatic organisms with 96-hour LC_{50} levels ranging from 0.1 to 3.4 ppm.

METHOMYL

I. INTRODUCTION

Methomyl is a broad-spectrum insecticide used on many vegetables, field crops, certain fruit crops, and ornamentals (Berg, et al. 1977). Introduced by DuPont in 1966 as an experimental insecticide-nematacide (Martin and Worthing 1974), methomyl is now manufactured by DuPont and Shell (Stanford Research Institute 1974) and used commercially as a foliar treatment to control aphids, army worms, cabbage looper, tobacco budworm, tomato fruitworm, cotton leaf perforator, and ballworm (Martin and Worthing 1974). About three million pounds (1360 tonnes) of methomyl were produced in the United States in 1974 under the trade name Lannate® (Pest Control, 1975). Wastes associated with methomyl production may contain methylene chloride. Methomyl formulations may contain pyridine as a contaminant (Sittig, 1977). Methomyl is highly soluble in water. Its bioconcentration factor is 1.0; octanol/water coefficient, 2.0 (see Table 1).

II. EXPOSURE

A. Water

Methomyl is considered stable in ground water and decomposes at a rate of less than 10 percent in 5 days in a river environment. In a lake environment, methomyl decomposes at a rate of less than 85 percent per year (U.S. EPA 1980).

B. Food

After the application of methomyl from 0.25 to 0.50 kilograms per hectare (kg/ha) on tomatoes, plant residues were below 0.2 ppm. Application of 1 kg/ha left residues of 0.3, 0.13, and 0.06 ppm at 1, 2, and 3 days, respectively, after spraying (Love and Steven, 1974). Methomyl applied at a rate of 3 oz/acre (0.2 kg/ha) left a 17 ppm residue on rape plants immediate-

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TABLE 1. PHYSICAL AND CHEMICAL PROPERTIES OF METHOMYL

Synonyms: S-methyl N-(methylcarbamoyl)oxy)thioacetamidate;
1-(methylthio)ethylideneamino methylcarbamate;
1-(methylthio)acetaldehyde O-methylcarbamoyloxime;
methyl N-(((methylamino)carbonyl)oxy)ethanimidothioate;
CAS Registry No. (16752-77-5); DuPont 1179; Lannate;
Mesomile; Nudrin

Chemical Formula: $(CH_3S)(CH_3)C{=}N{-}O(C{=}O)NHCH_3$

Molecular Weight: 162.2

Description: White crystal solid
Slight sulfurous odor
Soluble in organic solvents

Specific Gravity and/or Density d_4^{24} = 1.2946

Melting and/or Boiling Points: mp 78 to 79°C

Stability: Stable in aqueous solution
Subject to decomposition in moist soil
Overall degradation rate constant (0.01/day)

Half-life approximately 50 days

Solubility (water): 5.8 g/100 ml at 25°C

$$\frac{\text{sediment}}{H_2O} : \frac{.5}{1}$$

Vapor Pressure: 5×10^{-5} mm Hg at 25°C

Bioconcentration Factor (BCF) and/or
Octanol/water partition coefficient (K_{ow}): $K_{ow} = 2.0$
BCF = 1.0

Source: Martin and Worthing, 1974; Faircnild, 1977;
Windholz, 1976, U.S. EPA, 1980.

ly after application. This concentration declined rapidly to 1.5, 1.0, 0.4, and 0.2 ppm, 1, 2, 5, and 9 days later, respectively. Methomyl residues were not detected (less than 0.02 ppm) in seed harvested 22 days after application. Rape plant leaves collected after the application of methomyl at 3 to 4 oz/acre (0.2-0.3 kg/ha) had 2.5 to 16 ppm residues (Lee, et al. 1972).

Methomyl has a half-life in plants of 3 to 7 days. Harvey (1975) detected methomyl residue, its oxime, and small polar fractions one month after application. Methomyl residue standards for crops are noted in the Existing Guidelines and Standards Section of this report.

C. Inhalation and Dermal

Data are not available indicating the number of people exposed to methomyl by inhalation or dermal contact. Most human exposure would appear to occur during production and application. The U.S. EPA (1976) listed the frequency of illness among occupational groups exposed to pesticides. In 1157 reported cases, most illnesses occurred among ground applicators (229) and mixer/ loaders (142). The lack of or refusal to use safety equipment was a major factor of this contamination. Other groups affected were gardeners (101), field workers exposed to pesticide residues (117), nursery and greenhouse workers (75), soil fumigators in agriculture (29), equipment cleaners and mechanics (28), tractor drivers and irrigators (23), workers exposed to pesticide drift (22), pilots (crop dusters) (17), and flaggers for aerial application (6). Most illnesses resulted from carelessness, lack of knowledge of the hazards, and/or lack of safety equipment. Under dry, hot conditions workers tended not to wear protective clothing. Such conditions also tended generally to increase pesticide levels and dust on the workers.

III. PHARMACOKINETICS

A. Absorption and Distribution

Methomyl is a highly water-soluble carbamate insecticide which can be absorbed readily by moist mucous membranes or through the skin (Guerzoni, et al. 1976). Methomyl applied to the skin is less toxic than methomyl administered orally (Kaplan and Sherman, 1977). Kaplan and Sherman (1977) noted that there was no buildup of methomyl in fish after a 30-day feeding study, indicating that methomyl was not distributed or retained in any one specific organ of the body. In another study, there was no cumulative oral toxicity in rats (Harvey, et al. 1975). The investigators measured a total clearance rate of less than 24 hours after oral administration of methomyl to rats.

B. Metabolism

Harvey, et al. (1973) administered ^{14}C-labeled methomyl to rats. The radioactive methomyl was eliminated in the form of carbon dioxide, acetonitrile, and urinary metabolites. They noted the absence of methomyl, S-methyl N-hydroxythioacetimidate, methyl S,S'-dioxide, and conjugates of the former two compounds. Radiolabeled methomyl administered in the rat by Huntanen and Dorough (1976) also was metabolized to carbon dioxide and acetonitrile. Carbon dioxide was also found in soils treated with methomyl (Heywood 1975), without the presence of sulfoxide or sulfone (Baron 1978).

Han (1975) investigated the formation of nitrosomethomyl from cured meats containing methomyl and residual sodium nitrite. The samples were incubated under simulated stomach conditions (pH^2) for 1 and 3 hours. Nitrosomethyl was not found in the test material; the detection limit was less than 1 ppb.

C. Excretion

Methomyl is eliminated primarily through the urinary system (Harvey, et al. 1975).

IV. EFFECTS

A. Carcinogenicity

No evidence of methomyl carcinogenicity was observed in tests with rats and dogs (Kaplan and Sherman, 1977). Lijinsky and Schmaehl (1978) concluded that if nitrosomethyl carbamates (nitrosomethomyl) were formed by the reaction of the parent insecticide (methomyl) with nitrite in the environment or in the stomach, the carcinogenic risk of the parent compound could increase.

In pesticide workers, two cases of embryonal cell carcinoma have been associated with exposure to methomyl and three other pesticides (carbaryl, paration, and dimethoate). One of the pesticide workers underwent surgery for a testicular mass; the second worker died of metastatic embryonal cell carcinoma. These cases led the authors to suggest that testicular cancer may be related to agricultural chemical exposure (Prabhakar and Fraumeni, 1978).

B. Mutagenicity

Blevins, et al. (1977) screened methomyl and its nitroso derivative for mutagenic activity. Using histidine auxotrophs of S. typnimurium derived by Ames, they noted that methomyl, unlike its nitroso derivative, did not cause a significant increase in the number of revertant colonies in any of the strains used. Thus, while nitrosomethomyl appeared to be a potent mutagen, they considered methomyl to be non-mutagenic.

Querzoni, et al. (1976) tested methomyl for mutagenic activity on Saccharomyces cerevisiae. Methomyl was considered mutagenic at 50 ppm. The

authors noted, however, that the mutagenic effect depended on the S. cerevisiae strain.

C. Teratogenicity and Other Reproductive Effects

Methomyl was fed to pregnant New Zealand White rabbits on days 8 to 16 of gestation. Teratogenic effects were not found at any of three dietary levels, 0, 50, and 100 ppm (Kaplan and Sherman, 1977). The same authors also reported on a 3-generation, 6-litter reproduction study with rats with the same dietary levels. Methomyl did not have adverse effects on reproduction and lactation performance; in addition, pathological changes were not observed in the third-generation weanling pups. Using a model ecosystem, Howe (1978) did not see effects on quail egg production or egg fertility from a diet of 10, 40, and 80 ppm methomyl.

Blevins, et al. (1977) treated normal human skin cells with six insecticidal esters of N-methylcarbamic acid or their N-nitroso derivatives. The DNA of the cells was sedimented in alkaline sucrose gradients at various times after treatment. The insecticides used were aldicarb, baygon, (propoxur), BUX-TEN® (bufencab), carbofuran, landrin, and methomyl. Numerous singlestrand breaks were apparent in the DNA of all the nitroso derivative-treated cells but not in the DNA of those treated with the parent insecticides. The effect of the nitroso derivatives on the DNA could be observed for at least 20 hours after removal of the chemical from the cultures. The duration of effect suggested that the DNA-repairing events normally occurring in human cells after damage initiated by these chemical agents were different from repairing events which follow UV-type DNA damage or ionizing-type DNA damage in human cells. These observations suggest that the human cellular DNA in vivo is irreversibly altered by nitrosated N-methyl carbamate insecticides, resulting in numerous alkali-sensitive bonds (Blevins, et al. 1977).

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D. Chronic Toxicity

Rats of both sexes were fed nutritionally complete diets containing 0, 10, 50, 125, and 250 ppm of methomyl in a 90-day feeding study and 0, 50, 100, 200, and 400 ppm of methomyl in a 22-month feeding study. The weight gain for the high-dose males was significantly lower than that of controls. No clinical, hematological, biochemical, urinary, or pathologic evidence of toxicity was observed at 90 days. However, in the 22-month study, decreased Hb values were noted in the two higher-dose female test groups. A higher testis/body weight ratio was observed in the high-dose males. Histopathologic alterations were observed in kidneys of male and female rats receiving 400 ppm and in spleens of the female rats receiving 200 and 400 ppm of methomyl. Beagles of both sexes fed nutritionally complete diets containing 0, 50, 100, and 400 ppm of methomyl in 90-day and 2-year feeding studies showed no nutritional, clinical, urinary, or biochemical evidence of toxicity. In the 2-year study, an additional dietary level of 1000 ppm caused some clinical signs of toxicity and mortality. Similar to findings in the 22-month feeding study in rats, histopathologic changes were observed after 2 years in the kidney, spleen, and liver at the two higher feeding levels. Dogs receiving the high-level diet showed a compound-related anemia. Results of the long-term studies indicated that the no-effect level for rats and dogs was 100 ppm (Kaplan and Sherman, 1977).

E. Other Relevant Information

Several incidents of acute occupational exposure have been reported in the literature. In the first incident, four crews of field workers harvesting vegetables and fruits treated with pesticides including methomyl were studied. One crew had depressed blood cholinesterase activity

after harvesting corn treated with methomyl. Forty-eight percent of another crew had significant cholinesterase depression after harvesting treated citrus, tomatoes, and gladiolas (Owens, et al. 1978).

A second incident involved 120 grape pickers where 108 displayed symptoms suggesting pesticide poisoning. Methomyl and other cholinesterase-inhibiting pesticides, such as dimethorate and torak, were named in a legal complaint against the grower. The major symptoms claimed by the exposed workers were headache, dermatitis, vomiting, nausea, fatigue, and eye pain (McClure, 1976).

Kumagaya, et al. (1978) reported on two cases of poisoning from swallowing methomyl. The general symptoms were loss of consciousness, respiratory failure, miosis, myofibrillary twitching, increase in airway secretions, and reduced serum cholinesterase activity. Complications of pulmonary edema, hepatitis, and polyneuritis were also observed.

The oral LD_{50} values for rats, mice, ducks, and wild birds have been reported as 17, 10, 15, and 10 mg methomyl per kilogram body weight (mg/kg), respectively. The oral LD_{50} values for dogs, monkeys, guinea pigs, and chickens are reportedly 30, 40, 15, and 15 mg/kg, respectively. Inhalation LC_{50} values for rats, quails, and ducks are 77, 3680, and 1890 ppm, respectively. The dermal LD_{50} for rabbits is 5000 mg/kg. No adverse effects were noted when bobtail quail and albino rabbits were sprayed six times (at 5-day intervals) with 1.1 kg/ha of a 90 percent formulation of methomyl. Methomyl is relatively non-toxic to bees once the spray has dried (Fairchild, 1977; Martin and Worthing, 1974).

Carbamate pesticides, such as methomyl, have cholinergic properties similar to those of the organic phosphates, but of shorter duration. Methomyl inhibits both RBC and plasma cholinesterase activity. The period

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of inhibition of the cholinesterases is approximately 1-2 hours, and recovery usually occurs between 24 and 48 hours after contact. Atropine administration is the treatment of choice (Simpson and Bermingham, 1977).

V. AQUATIC TOXICITY

A. Acute and Chronic Toxicity

Methomyl 24-hour TL_m (median toxic limit) values for carp (Cyprinus carpio) and tilapia fish range from 1.054 to 3.16 mg/l (El-Refai, et al. 1976). The LC_{50} (96-hour exposure) for rainbow trout (Salmo gainneri) was 3.4 ppm; for bluegill (Lepomis macrochirus), 0.87 ppm; and for goldfish (Carrasius auratus), greater than 0.1 ppm (Martin and Worthing, 1974). Following exposure (4-48 hours) of marine or estuarine fishes to carbamate pesticide, the acetylcholinesterase activity in the brain was inhibited by 77 to 89 percent (Coppage, 1977).

B. Plant Effects and Residues

Pertinent data could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The threshold limit value for air is established at 2.5 mg/m^3 (Fairchild, 1977). The Office of Water and Waste Management is in the process of conducting preregulatory assessment of methomyl under the Safe Drinking Water Act. The Office of Toxic Substances has promulgated regulations for methomyl under Section 3 of the Federal Insecticide, Fungicide and Rodenticide Act.

Methomyl residue concentrations in crops are regulated as follows: 0.1 ppm for lentils and pecans; 1 ppm for forage, hay, barley (grain), and oats (grain); 2 ppm for strawberries and avocados; 5 ppm for chinese cabbage; 6 ppm for blueberries, beets, collard, dandelions, kale,

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mustard greens, parsley, swiss chard, turnip greens, and watercress; 10 ppm for wheat, rye, barley, and oats used as hay, straw, or forage; and 40 ppm for bermuda grass hay (Federal Register [43(98): 21700, 1978; 43 and (112): 25120, 1978; 44(63): 18972; 44(83): 24846; 44(129): 38844; 44(160): 47934, and 44(227): 67117, 1979]):

B. Aquatic -

Guidelines or standards to protect aquatic life could not be located in the available literature.

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No. 126

Methyl Alcohol

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

Methyl alcohol, CH_3OH, also called methanol, is the first member of a homologous series of monohydric aliphatic alcohols. At room temperature, methyl alcohol is a colorless, neutral liquid possessing a mild distinctive odor. [1] Additional chemical and physical properties of methyl alcohol are presented in Table XIII-1. [2,3,4]

The greater part of methyl alcohol manufactured in the US is produced synthetically. [5] One widely used synthetic process is the "medium pressure process" which involves the reduction of carbon monoxide (containing small amounts of carbon dioxide) with hydrogen. The reduction step is carried out at 250-400 C and at 100-600 atmospheres pressure using a catalyst. [1]

During the years 1968-73, synthetic methyl alcohol production in the US increased at an average annual rate of over 13.2%. In 1973, the production of synthetic methyl alcohol amounted to slightly over seven billion pounds, around one billion gallons. In addition, an estimated 10 million pounds (1.5 million gallons) of "natural" (eg, from wood distillation) methyl alcohol were produced. [5]

Methyl alcohol is used in a variety of industrial processes. The major use is in the production of formaldehyde which amounted to 39% of the methyl alcohol consumed in the US in 1973. [5] Other commercial uses of methyl alcohol are in the production of chemical derivatives, such as dimethyl terephthalate, methyl halides, methyl methacrylate, acetic acid, and methylamines, and because of its solvent properties, methyl alcohol is

also used in paints, varnishes, cements, and other formulations such as inks and dyes. [1,5] Table XIII-2 lists the consumption of methyl alcohol by product and quantity produced in the US for the year 1973. [5]

A number of occupations with potential exposure to methyl alcohol are listed in Table XIII-3. [6]

NIOSH estimates that approximately 175,000 workers in the US are potentially exposed to methyl alcohol.

EFFECTS ON HUMANS

Burk [26] attributed the toxic effects of methyl alcohol to formaldehyde and formic acid, indicating that both compounds were oxidation products of methyl alcohol. The author stated that the diagnosis of methyl alcohol poisoning is sometimes very difficult, and would be more easily verified by quantitative determinations of formic acid in the urine of persons suspected of being poisoned with methyl alcohol.

Percutaneous absorption of methyl alcohol can lead to serious consequences, including death. In 1968, Gimenez et al [27] reported an analysis of 19 cases of children, ranging in age from 1.5 months to 4 years, who were poisoned as a result of having cloths soaked in methyl alcohol applied to their abdomens to relieve gastrointestinal troubles or other unspecified complaints. There were 2 additional cases reviewed in which both methyl and ethyl alcohols had been employed in this way, making a total of 21 cases. Although absorption of methyl alcohol via the respiratory tract was possible in these cases, the fact that the cloths were held in place by rubber baby pants would favor percutaneous absorption of the alcohol as the significant route of exposure. The length of time between application and onset of symptoms of intoxication was 1-13 hours (7 1/4 hours average). The early signs of intoxication were described by the authors as central nervous system depression with 13 children having

exhibited severe respiratory depression and 11 of these having convulsions. Blood pH in the 21 patients ranged from 6.4 to 7.38 (normal: 7.36-7.41 [28]), indicating acidosis in most cases. Twelve of the 21 children died of cardiac or respiratory arrest 2-10 days after hospital admission. The survivors recovered without apparent permanent damage. Papilledema and ocular fundus bleeding were observed in 2 of the infants who subsequently died. Abdominal skin lesions were present in 5 patients, 3 of the erythematous type and 2 of the scaling type. The authors [27] commented that while there was no relationship between methyl alcohol blood levels as tested in 11 children (57-1,130 mg%) and prognosis, there was a relationship between the initial blood pH and the subsequent course of the illness. In general, treatment consisted of administering sodium bicarbonate, glucose, ethyl alcohol, fluids, and electrolytes. Other forms of treatment included peritoneal dialysis, exchange transfusion, mechanical respiration, and the administration of anticonvulsant drugs. It must be pointed out that the absorptive properties of the skin of infants are probably different from those of adults and consequently infant susceptibility to, and manifestations of, methyl alcohol intoxication may not parallel those seen in adults.

In 1952, Leaf and Zatman [30] reported on experiments in which 5 male volunteers ingested 2.5-7.0 ml of methyl alcohol diluted to 100 ml with water. These amounts of methyl alcohol corresponded to doses of 29-84 mg/kg. Two blood samples were taken from 3 subjects, 2-5 hours after the ingestion. Urine was collected frequently for 11-16 hours following methyl alcohol administration. Both the blood and urine samples were analyzed for methyl alcohol by a colorimetric method based on the oxidation of methyl alcohol to formaldehyde and formation of a colored complex with a modified Schiff's reagent. The results of this experiment indicated that under these conditions methyl alcohol was rapidly absorbed from the gastrointestinal tract. The maximum methyl alcohol concentration in the urine was achieved approximately one hour after ingestion and then decreased exponentially. The ratio of blood to urine methyl alcohol

concentrations remained almost constant for the 3 subjects in which it was determined, and the authors [30] concluded that the change in the concentration of methyl alcohol in the urine was an accurate indicator of the change in methyl alcohol concentration in the body. At the levels used in this experiment, the concentration of methyl alcohol in the urine declined to control values within 13-16 hours after ingestion. Leaf and Zatman [30] also stated that only 0.4-1.2% of the ingested methyl alcohol was eliminated unchanged in the urine.

In another experiment in the same study, [30] 2 male volunteers ingested 15 ml of ethyl alcohol and 4 ml of methyl alcohol simultaneously. They then ingested 10 ml of ethyl alcohol every hour for the next 7 hours. The same individuals served as their own controls in a previous experiment in which they ingested only 4 ml of methyl alcohol. Urine was collected hourly and analyzed for methyl alcohol. The maximum urinary methyl alcohol concentrations for those individuals who ingested both methyl alcohol and ethyl alcohol were 8.82 and 9.20 mg/100 ml, compared to values of 6.05 and 5.50 mg/100 ml when methyl alcohol alone was ingested. Moreover, the total amount of methyl alcohol excreted unchanged in the urine in the first 7 hours after ingestion was 107.1 mg and 125.5 mg (3.7 and 3.96% of the administered dose respectively) when both methyl alcohol and ethyl alcohol were ingested, whereas only from 18.2 to 30.8 mg (0.57-0.97% of the administered dose) was excreted unchanged in a similar time period after ingestion of 4 ml methyl alcohol alone. The authors [30] concluded that in humans ethyl alcohol interfered with the normal oxidation of methyl alcohol, causing more of it to be excreted unchanged in the urine. Moreover, according to the authors' conclusion, higher concentrations of methyl alcohol in the blood are maintained in the presence of ethyl alcohol at any given time after absorption, as compared to concentrations achieved in the absence of ethyl alcohol.

Ethyl alcohol may inhibit the oxidation of methyl alcohol in vivo by competing (competitive inhibition) for the alcohol dehydrogenase system. It is conceivable, therefore, that chronic alcoholics might exhibit measurable concentrations of methyl alcohol in the blood or urine even though they have not been exposed to methyl alcohol.[37]

In summary, an integration of in vitro [33-35] and in vivo studies [29-31,37] indicates that in humans methyl alcohol is oxidized primarily by alcohol dehydrogenase. The results discussed in the section on Animal Toxicity, however, suggest that in nonprimates methyl alcohol is oxidized primarily by the catalase-peroxidase system.

ANIMAL TOXICITY

Gilger and Potts [42] concluded from their studies that the results of oral administration of methyl alcohol to rats, rabbits, and dogs differed from those reported on humans in 4 important areas, namely, lethal dose, time course of development and signs of intoxication, eye effects, and acidosis. The authors also concluded that, following intoxication with methyl alcohol, the responses of primates more closely approximated human responses than did those of nonprimates. An extensive review of the literature dealing with the oral toxicity of methyl alcohol in humans and nonprimates was supportive of their conclusion. The authors concluded that the approximate lethal oral dose of methyl alcohol in humans (0.85-1.4 g/kg) was 1/3 the equivalent dose in monkeys and 1/9 the equivalent dose in rats. Moreover, nonprimates exhibited severe early intoxication with narcosis lasting until death whereas primates showed much less early intoxication followed by a symptomless latent period, then by sickness and death. The only eye changes observed with certainty in nonprimates were early pupillary changes and corneal opacities following exposure keratitis. Some monkeys, however, and many humans developed partial or complete

blindness accompanied by eyeground changes such as hyperemia of the optic discs and venous engorgement. Finally, humans and monkeys often developed severe acidosis (CO_2-combining capacity less than 20 volumes %) after methyl alcohol ingestion; this condition was rare in nonprimates and occurred only at near lethal or lethal doses.

Correlation of Exposure and Effect

Well-documented studies that correlate environmental levels of methyl alcohol with observed toxic effects have not been found in the literature, nor have any long-term epidemiologic studies of chronic low-level occupational exposure been found.

Effects seen from either of the 2 most common routes of occupational exposure (inhalation and percutaneous absorption) include: headache [14,16,17,39]; dizziness [13,19]; nausea [16,17,26]; vomiting [17]; weakness (unspecified) [16]; vertigo [17,26]; chills [13]; shooting pains in the lower extremities [13]; unsteady gait [17]; dermatitis [14]; multiple neuritis characterized by paresthesia, numbness, prickling, and shooting pain in the back of the hands and forearms, as well as edema of the arms [15]; nervousness [19]; gastric pain [19]; insomnia [19]; acidosis [19]; and formic acid in the urine. [26] Eye effects, such as blurred vision, [16,17] constricted visual fields, [17,19,25] blindness, [13,25] changes in color perception, [17] double vision, [19] and general visual

disturbances [17] have been reported. Eye examinations have shown sluggish pupils, [13,17] pallid optic discs, [13] retinal edema, [17] papilledema, [26] hyperemia of the optic discs with blurred edges and dilated veins. [17]

The study by Bennett et al [40] showed similar symptoms resulting from ingestion. These are acidosis, headache, visual disturbances, dizziness, nausea and vomiting, severe upper abdominal pain, dilated and nonreactive pupils. Eyeground examinations showed hyperemia of the optic discs and retinal edema. The eyeground changes were almost always found in acidotic patients. This finding is suggestive of a correlation between acidosis and visual disturbances. However, a number of patients, with and without acidosis, complained of visual disturbances. Additionally, blood tests showed elevated serum amylase levels in 14 of 21 patients. This finding in conjunction with complaints of upper abdominal pain and pancreatic necrosis seen at autopsy led the authors [40] to conclude that hemorrhagic pancreatitis resulted from acute methyl alcohol intoxication. However, reports of acute hemorrhagic pancreatitis by parenteral routes have not been found.

Direct skin contact with methyl alcohol has been said to cause dermatitis, [14] erythema, and scaling. [27] The reported variability in susceptibility [14] is probably largely because of variations in time of contact with methyl alcohol; it is evident that sufficient dermal contact with any lipid solvent such as methyl alcohol has the potential for causing skin irritation.

Basis for the Recommended Environmental Standard

Epidemiologic studies incorporating comprehensive environmental surveys, well-planned surveillance, a sufficient study population, and statistical analysis have not been found in the literature. It is therefore difficult to recommend an environmental limit based upon unequivocal scientific data.

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TABLES AND FIGURE

TABLE XIII-1

PHYSICAL AND CHEMICAL PROPERTIES OF METHYL ALCOHOL

Molecular formula	CH_3OH
Formula weight	32.04
Apparent specific gravity at 20 C	0.7910
Boiling point at 760 mmHg	64.5 C
Vapor pressure at 20 C	96 mmHg
Melting point	-97.6 C
Solubility in water	Miscible
Solubility in alcohols, katones, esters, and halogenated hydrocarbons	Miscible
Flash point, Tag open cup	16 C
Flash point, Tag closed cup	12 C
Flammable limits (% in air)	6.72-36.50
Vapor density (air=1)	1.11
Corrosivity	Noncorrosive at normal atmospheric temperatures. Exceptions: lead and aluminum
Conversion factors (760 mmHg and 25 C)	1 ppm=1.310 mg/cu m 1 mg/cu m=.763 ppm

Adapted from ANSI Z37 [2], the Manufacturing Chemists Association [3], and the Handbook of Chemistry and Physics [4]

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TABLE XIII-2

US METHYL ALCOHOL CONSUMPTION, 1973

	Million Pounds	Million Gallons
Formaldehyde	2,778	420
Dimethyl terephthalate	435	66
Solvent usage	565	85
Methyl halides	435	66
Methylamines	232	35
Methyl methacrylate	265	40
Inhibitor for formaldehyde	66	10
Exports	824	124
Glycol methyl ethers	81	12
Acetic acid	240	36
Miscellaneous	1,207	181
Total	7,128	1,075

From Blackford [5]

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TABLE XIII-3

POTENTIAL OCCUPATIONAL EXPOSURES TO METHYL ALCOHOL

Acetic acid makers
Adhesive workers
Alcohol distillery workers
Alcohol lamp users
Aldehyde pumpmen
Antifreeze workers
Art glass workers
Automobile painters
Aviation fuel handlers
Bookbinders
Bronzers
Brushmakers
Denatured alcohol workers
Dimethyl sulfate makers
Drug makers
Drycleaners
Dye makers
Dyers
Ester makers
Explosives workers
Feather workers
Felt-hat makers
Flower makers, artificial
Formaldehyde makers
Foundry workers
Furniture polishers
Gilders
Glassmakers, safety
Hectograph operators
Incandescent lamp makers
Inkmakers
Japan makers
Japanners
Jet fuel workers
Lacquerers
Lacquer makers
Lasters
Leather workers
Linoleum makers
Lithographers
Metal polishers
Methyl acrylate makers
Methyl alcohol workers
Methyl amine makers
Methylation workers
Methyl bromide makers
Methyl chloride makers
Methyl methacrylate makers
Millinery workers
Motor fuel blenders
Organic chemical synthesizers
Painters
Paintmakers
Paint remover workers
Patent leather makers
Perfume makers
Photoengravers
Photographic film makers
Polish makers
Printers
Rayon makers
Resin makers
Rocket fuel handlers
Rocket fuel makers
Rubber shoe cementers
Rubber workers
Shellackers
Shellac makers
Shoe factory workers
Shoe finishers
Shoe heel coverers, wood
Shoe stitchers
Soapmakers
Straw-hat makers
Sugar refiners
Textile printers
Type cleaners
Vacuum tube makers
Varnish workers
Vulcanizers
Wood alcohol distillers
Wood stainers
Wood stain makers

From Gafafer [6]

TABLE XIII-4

ANIMAL EXPERIMENTATION RESULTS
OF METHYL ALCOHOL EXPOSURE

Species	Route of Exposure	Dose	Effect	Reference
Monkeys	Inhalation	5,000 ppm duration unknown	The monkey survived for an unstated period of time.	47
"	"	1,000 ppm duration unknown	The monkey died promptly upon exposure at this level.	47
Dogs	"	450-500 ppm 8 hr/day 7 days/week for 379 days	Blood levels of methyl alcohol were found to range from 10 to 15 mg/100 ml of blood and on occassion went as high as 52 mg/100 ml. No abnormal eye findings were reported.	41
"	Oral	2.5 to 9.0 g/kg body weight	Of the 9 treated dogs, 2 died at doses of 4 and 9 g/kg. C02 combining capacities dropped below normal in 2 dogs, and no ophthalmoscopic changes were noted.	42

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TABLE XIII-4 (CONTINUED)

ANIMAL EXPERIMENTATION RESULTS
OF METHYL ALCOHOL EXPOSURE

Species	Route of Exposure	Dose	Effect	Reference
Monkeys	Oral	1.0 to 8.0 g/kg	Acidosis developed in monkeys receiving doses ranging from 3.0 to 6.0 g/kg. The animal receiving 1.0 g/kg did not develop acidosis. Definite eye-ground change occurred to 2 of the acidotic monkeys.	42
Rats	"	4.75 g/kg	70% mortality	42
"	"	4.5 g/kg	None of the 9 tested rats developed acidosis.	42
Rabbits	"	3.5 g/kg	One animal receiving this dose died in less than 24 hours. No eye fundus changes were reported.	42
Rabbits	"	2.1 g/kg	Of the 3 animals tested at this dose, all died between 24 hours and 3 days after dosing.	42
"	Intra-cutaneous	10 mg and 35 mg	At 10 mg, there was no skin reaction, whereas at 35 mg, a 9-sq mm skin reaction occurred.	49

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TABLE XIII-4 (CONTINUED)

ANIMAL EXPERIMENTATION RESULTS
OF METHYL ALCOHOL EXPOSURE

Species	Route of Exposure	Dose	Effect	Reference
Monkeys	i.p. inj	0.5 g/kg of 14 C-methyl alcohol with an equimolar amount of ethyl alcohol	The ethyl alcohol reduced the oxidation of methyl alcohol 90%.	52
"	"	1.0 g/kg 14 C-methyl alcohol and 6.0 g/kg 14C-methyl alcohol	The methyl alcohol was oxidized at a rate of 37 mg/kg/hour between the first and fourth hour. The CO2 formation was linear at the high dose; the oxidation rate was 47 mg/kg/hour which is a significant difference.	52
Rats	"	1.0/kg 14C-methyl alcohol	The oxidation rate of the methyl alcohol was 24 mg/kg/hr for the first 28 hours. At the end of 36 hours 77% of the methyl alcohol had been oxidized to 14C-labled CO2 and 24% was excreted unchanged in approximately equal amounts by the pulmonary and combined urinary and fecal routes.	51

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No. 127

S,S'-Methylene - o,o,o',o'-Tetraethyl Phosphorodithioate

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

PHOSPHORODITHOIC ACID,

S,S'-METHYLENE,O,O,O',O'-TETRAETHYL ESTER (ETHION)

Summary

The S,S'-methylene,O,O,O',O'-tetraethyl ester of phosphorodithoic acid, ethion, has not shown mutagenic effects in mice or teratogenic effects in fowl. Subcutaneous injection of the compound into atropinized chickens produced neurotoxic effects. There is no available information on the possible carcinogenic effects of ethion.

Ethion has shown acute toxicity in stonefly naiads at a 96-hour LC_{50} range from 1.8 to 4.2 µg/l.

I. INTRODUCTON

O,O,O',O'-Tetraethyl-S,S'-methylene bisphosphorodithioate (CAS registry number 563-12-2), also called ethion, is an insecticide and miticide made from phosphorus pentasulfide (SRI, 1976). Ethion has the following physical and chemical properties (Windholz, 1976; FAO, 1969):

Formula:	$C_9H_{22}O_4P_2S_4$
Molecular Weight:	384.48
Melting Point:	-12°C to -13°C
Density:	1.220^{20}_{4}
Vapor Pressure:	Practically non-volatile at ordinary temperatures
Solubility:	Insoluble in water, soluble in organic solvents
Consumption:	0.7 million lbs/year (SRI, 1976)

Ethion is a pre-harvest topical insecticide used primarily on citrus fruits, deciducus fruits, nuts and cotton (SRI, 1976). It is also used as a cattle dip for ticks and as a back-line treatment for buffalo flies (FAO, 1969).

II. EXPOSURE

A. Water

Pertinent data could not be located in the available literature. Water contamination from ethion manufacturing may be minimal due to the common use of industrial wastewater treatment plants (U.S. EPA, 1977).

B. Food

Residues on a variety of foods have been reported (FAO, 1969). A samoling shows the residues on fruits and vegetables range from 10.4 ppm for raisins to less than 0.1 ppm for almonds. The majority are less than 1 ppm. Treated cotton showed no residue in the seed. Tea at harvest snowed residues of up to 7 ppm; since tea is blended prior to sale, residues are lower

when consumed. Lactating cows fed up to 20 ppm radioactive ethion showed no residues in their milk. In meat, the highest radioactivity was in the liver; however, chemical analysis showed these residues were not ethion but metabolites. When animals were dipped, residues from skin absorption of ethion were found in the body fat.

C. Inhalation and Dermal

Pertinent data could not be located in the available literature.

III. PHARMACOKINETICS

A. Absorption

Results of acute toxicity studies in animals indicate that ethion is absorbed following oral and dermal exposure (Gaines, 1969).

B. Distribution

Following feeding of dairy cattle with ethion, small amounts of the unchanged compound were found in milk and fatty tissues (Vettorazzi, 1976).

C. Metabolism

Rao and McKinley (1969) have reported that <u>in vitro</u> metabolism of ethion occurs through oxidative desulfuration of the compound by chicken liver homogenates.

D. Excretion

Pertinent data could not be located in the available literature. Based on studies of other organophosphorous insecticides, it may be anticipated that ethion metabolites would be eliminated primarily in the urine (Matsumura, 1975).

IV. EFFECTS

A. Carcinogenicity

Pertinent data could not be located in the available literature.

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B. Mutagenicity

Vettorazzi (1976) has cited an unpublished study which found no dominant lethal effects in mice administered ethion.

C. Teratogenicity

Oral administration of ethion (100 ppm) to chickens, chukars, and quail failed to produce teratogenic or adverse reproductive effects (Abbott and Walker, 1972).

D. Other Reproductive Effects

Oral feeding of ethion to chickens, chukar, and quail failed to affect egg hatch (Abbott and Walker, 1972).

E. Chronic Toxicity

Subcutaneous injection of atropinized chickens with 400 mg/kg ethion produced neurotoxic effects (flaccid paralysis) (Gaines, 1969). Ethion will produce anti-cholinesterase effects in mammals (Vettorazzi, 1976).

V. AQUATIC TOXICITY

A. Acute Toxicity

Sanders and Cope (1968) observed 96-hour LC_{50} values ranging from 1.8 to 4.2 µg/l for stonefly naiads (Pteronarcys californica) exposed to ethion.

B. Chronic Toxicity, Plant Effects and Residues

Pertinent data could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The World Health Organization (FAO, 1969) has established an ADI level of 0.005 mg/kg for ethion based on cholinesterase inhibition studies.

B. Aquatic

Pertinent data could not be located in the available literature.

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No. 128

Methyl Ethyl Ketone

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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Methyl Ethyl Ketone

I. INTRODUCTION

Methyl ethyl ketone or (MEK) as it is commonly referred to is a clear, colorless, volatile liquid (VP of 100 mm at 25°C) with a molecular weight of 72.12. It has a melting point of -86.35°C and a boiling point of 76.6°C. It is very soluble in water (25.5 g/100 at 2 percent) and soluble in all proportions in alcohol, ether, acetone and benzene.[2] It is also highly flammable (22°F - open cup).[3]

MEK is produced and used as a solvent in nitrocellulose coatings and vinyl films; in the synthesis of colorless resins; in the manufacture of smokeless powder; in paint removers, cements, adhesives, and cleaning fluids; in printing industry; as a catalyst carrier; in lube oil dewaxing and in acrylic coatings.[2]

II. ROUTES OF EXPOSURE

MEK is rapidly absorbed through the skin by inhalation.

III. PHARMACOKINETICS

MEK occurs in trace amounts in normal human urine and may have a dietary origin.[1] Most probable precursor is - methylacetoacetic acid.[1]

Urine of rabbits exposed to MEK reported to contain glucuronide of 2-butanol.[1]

IV. EFFECTS ON MAMMALS

The chief effect of MEK is narcosis but is also a strong irritant of the mucous membranes of the eyes and nose. The oral LD50 for rats is 3.3 g/kg and the inhalation LC50 is

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around 700 ppm.[1]

Repeated exposure of guinea pigs for 12 weeks to 235 ppm caused no symptoms.[1]

Lethal doses in animals caused marked congestion of internal organs and slight congestion of brain. Lungs showed emphysema (see Table 1).

Slight throat irritation in humans occured at 100 ppm and in eyes at 200 ppm.

Dermatoses among workers having direct contact and exposed to vapors are not uncommon. Some workers complained of numbness of fingers and arms.[1]

Table 1

Effects of Methyl Ethyl Ketone on Animals

	Concentration/ Duration	Animal	Effects
Methyl Ethyl Ketone	33,000-100,000 ppm/200 min.	Guinea Pigs	Gasping, death, emphysema, slight congestion of the brain, marked congestion of the systemic organs especially the lungs and corneal opacities
	3,300 ppm/810 min.	Guinea Pigs	No abnormal signs
	1,125 ppm/24 hr/3,55d	Rats	No evidence of peripheral neuropathy
	1,126 or 2,618 ppm/7 hr/d on d 6-15 of gestation	Pregnant Rats	Embryotoxicity, fetotoxicity and possible teratogenicity

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No. 130

Methyl Methacrylate

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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METHYL METHACRYLATE

Summary

Oral or skin painting studies in rats have failed to show carcinogenic effects of administration of methyl methacrylate. Implantation of the compound in mice also failed to produce tumors.

Exposure of rats to a mixture of chloroprene and methyl methacrylate produced an increase in lymphocyte chromosome aberrations. Increased chromatid breaks and chromosome breaks have been reported in workers exposed to this same chemical mixture.

Teratogenic effects (hemangiomas) have been reported following intraperitoneal administration of methyl methacrylate to pregnant rats. Inhalation exposure of pregnant rats to an acrylic cement containing methyl methacrylate failed to produce significant teratogenic effects.

Ninety-six hour LC_{50} values for four species of fish range from 159 to 368 ppm. Inhibition of cell multiplication of an alga begins at 120 ppm.

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I. INTRODUCTION

Methyl methacrylate, CAS registry number 80-62-6, is a colorless, clear, volatile liquid. It is made from acetone cyanohydrin which is hydrolyzed in sulfuric acid to yield methacrylamide sulfate, which is then treated with methanol to yield methyl methacrylate. It has the following physical and chemical properties (Windholz, 1976; Hawley, 1971; Weast, 1972; Verschueren, 1977):

Formula:	$C_5H_8O_2$
Molecular Weight:	100.12
Melting Point:	-48.2°C
Boiling Point:	101°C
Density:	0.9440^{20}_{4}
Vapor Pressure:	28 torr @ 20°C
Solubility:	Sparingly soluble in water, miscible in alcohol, benzene, ether, etc.
Production:	706 million lbs (1973) (Gruber, 1975)

Virtually all the methyl methacrylate produced in this country is used for polymers, e.g., surface coating resins and plastics (plexiglass, lucite), ion exchange resins, dentures, etc.

II. EXPOSURE

A. Water

According to Gruber (1975), about 1.8 g of methyl methacrylate per kilogram final product (methyl methacrylate) is present in wastewater. The amount of methyl methacrylate entering domestic water supplies is probably small.

B. Food

Polymethyl methacrylate is used for food storage. A very small amount of residual monomer may migrate into food from the polymer.

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C. Inhalation

Fugitive emissions from production, storage, and transportation probably constitute the only major sources of methyl methacrylate in the air. The concentration would most likely be highest in production facilities. Production was estimated to be 7.9 million pounds in 1974 (U.S. EPA, 1976). A 550-million pound-per-year production facility with 0.5 percent loss emits 39.6 grams of methyl methacrylate per second. If this is considered to be a virtual point source, the downwind concentration 500 meters away would be 1.5 ppm one-hour average (U.S. EPA, 1976).

D. Dermal

Pertinent data could not be located in the available literature.

III. PHARMACOKINETICS

A. Absorption and Distribution

Pertinent data could not be located in the available literature.

B. Metabolism

Bratt and Hathway (1977) found that up to 88 percent of a single methyl(^{14}C)methacrylate dose of 5.7 mg/kg body weight was expired as CO_2 within 10 days. Neither the route of administration nor the specific labelling of the propylene residue changed this value. Small amounts of several metabolites were excreted in the urine, including ^{14}C-methylmalonate, ^{14}C-succinate, 2-formylpropionate, and possibly ^{14}C-β-hydroxybutyrate.

Corkill, et al. (1976) found that the disappearance of methyl methacrylate in human blood *in vitro* showed a first order dependence on methyl methacrylate concentration. The calculated half-life was 20 to 40 minutes, irrespective of the sex or age of the blood donor. More than 40 percent of the initial dose of methyl methacrylate was converted to methacrylic acid within 90 minutes.

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C. Excretion

Pertinent data could not be located in the available literature.

IV. EFFECTS

A. Carcinogenicity

The International Agency for Research on Cancer (IARC, 1979) has evaluated the available data and concluded that there is not enough information to determine the potential carcinogenicity of methyl methacrylate to humans. Borzelleca, et al. (1964) observed no treatment-related tumors in male and female Wistar rats administered 6, 60, or 2,000 mg/l methyl methacrylate in their drinking water for two years. Oppenheimer, et al. (1955) found no local tumors in ten Wistar rats painted with methyl methacrylate three times per week for four months and observed for their entire life span.

Another study, by Spealman, et al. (1945), in which male and female mice received implants consisting of 0.075 gm of methyl methacrylate in a gelatin capsule also yielded negative results.

B. Mutagenicity

The only data available on the mutagenic effects of methyl methacrylate are two studies involving exposure to a mixture of chloroprene and methyl methacrylate (Bagramjan, et al. 1976; Bagramjan and Babajan, 1974). In both studies, an increased frequency of chromosomal aberrations were found in rats exposed to the mixture. Bagramjan, et al. (1976) also measured a significant increase in chromatid breaks and chromosome breaks in the lymphocytes of workers exposed to a mixture of chloroprene and methyl methacrylate.

C. Teratogenicity

Singh, et al. (1972a,b) and Autian (1975) injected intraperitoneally three groups of pregnant Sprague-Dawley rats with methyl methacrylate at doses of 0.1, 0.2, or 0.4 g/kg body weight on days 5, 10, and 15 of ges-

tation. In animals administered the two higher doses, a significantly greater number of hemangiomas were seen at various sites. All three groups exhibited reduced fetal weights, but no significant increase in skeletal defects was observed in any group.

McLaughlin, et al. (1978) exposed pregnant mice to a vapor concentration of 1,330 ppm methyl methacrylate (as acrylic cement, Simplex p) for two hours two times per day for days 6 through 15 of gestation. No fetotoxic or teratogenic effects were noted other than a slight decrease in the average fetal weight.

D. Other Reproductive Effects

Pertinent data could not be located in the available literature.

E. Chronic Toxicity

Spealman, et al. (1945) conducted a series of subchronic inhalation ex- periments involving guinea pigs and dogs. Guinea pigs exposed to 39.0 mg/l methyl methacrylate for two hours per day for three days exhibited significant liver degeneration, while dogs exposed to 46.8 mg/l methyl methacrylate for two hours per day for 8 to 15 days exhibited liver degeneration and tubular degeneration of the kidneys.

Borzelleca, et al. (1964) administered 6, 60, and 2,000 ppm of methyl methacrylate in drinking water to male and female rats for a period of two years. Weight gain was decreased for the first few weeks in animals given the highest dose. No changes in hematological values or urine concentrations of protein and reducing agents were noted. Females receiving the highest dose level exhibited an increase in kidney to body weight ratios.

Blagodatin, et al. (1970) reported symptoms of headache, pain in the extremities, fatigue, sleep disturbance, loss of memory, and irritability in 152 workers exposed to concentrations of 0.5 to 50 ppm methyl methacrylate. Most of the workers had been employed for longer than 10 years.

F. Acute Toxicity

No detectable acute effects were noted in workers employed in manufacturing polymethyl methacrylate sheets (Cromer and Kronoveter, 1976). The airborne concentrations of methyl methacrylate varied from 4 to 49 ppm.

V. AQUATIC TOXICITY

A. Acute Toxicity

Pickering and Henderson (1966) observed the following 96-hour LC_{50} values for fish exposed to methyl methacrylate: fathead minnow (Pimephales promelas) - 159 ppm in soft water (20 mg/l); fathead minnow - 311 ppm in hard water (360 mg/l); bluegill (Lepomis macrochirus) - 357 ppm in soft water (20 mg/l); goldfish (Carassius auratus) - 277 ppm in soft water (20 mg/l); guppies (Lebistes reticulatus) - 368 ppm in soft water (20 mg/l).

B. Chronic Toxicity

Pertinent data could not be located in the available literature.

C. Plant Effects

Inhibition of cell multiplication of the alga, Microcystis aerugi-nosa, by methyl methacrylate begins at 120 ppm (Bringmann and Kuhn 1976).

D. Residues

Pertinent data could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

Guidelines have been established for exposure to methyl methacry-late by the American Conference of Governmental Industrial Hygienists and OSHA. Both the TLV and the federal standard have been set at 100 ppm (or 410 mg/m^3) (ACGIH, 1977; 29 CFR 1910).

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B. Aquatic

No guidelines have been established for the protection of aquatic organisms from acute or chronic methyl methacrylate toxicity because of the lack of pertinent data.

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No. 131

Naphthalene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

NAPHTHALENE

Summary

Naphthalene is present in ambient water as well as drinking water. Naphthalene can be absorbed by any route, although the efficiency of absorption has not been determined. The toxicological properties are due to the formation of highly reactive metabolites. Chronic exposure produces cataracts, hemolytic anemia, and kidney disease. Naphthalene can cross the placenta and produce these effects on newborns. Napnthalene has been found to be nonmutagenic in several microsomal/bacterial assay systems. Chronic toxicity studies of naphthalene have shown it to be noncarcinogenic.

Naphthalene has been shown to be acutely toxic in freshwater fish with LC_{50} values of 150,000 µg/l being reported in one static bioassay. Freshwater invertebrates were more sensitive with LC_{50} values of 8,570 µg/l, as were marine fish with LC_{50} values ranging from 2,350 to 2,600 µg/l.

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INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Naphthalene (U.S. EPA, 1979).

Naphthalene ($C_{10}H_8$; molecular weight 128.16) is a bicyclic, aromatic hydrocarbon which in a pure grade, forms a white crystalline solid at room temperature (Windholz, 1976). Pure naphthalene has a melting point of 80.2°C, a boiling point of 217.96°C (Manufacturing Chemists Assoc., 1956) and a vapor pressure of 0.0492 mm Hg at 19.8°C (Gil'denblat, et al. 1960). Naphthalene is water soluble, with solubility ranging from 30,000 µg/l (Mitchell, 1926) to 40,000 µg/l (Josephy and Radt, 1948). Naphthalene vapor and dust can form explosive mixtures with air (Windholz, 1976). Naphthalene is used as an intermediary in the production of dye compounds, in the formulation of solvents, lubricants and motor fuels, and as a feedstock in the synthesis of phthalic anhydride. Naphthalene is also used directly as a moth repellant, insecticide, antihelminthic, vermicide, and an intestinal antiseptic (U.S. EPA, 1979). In 1974, production of naphthalene was approximately 2.9 x 10^5 metric tons (U.S. EPA, 1976).

II. EXPOSURE

A. Water

The two major sources of naphthalene in the aquatic environment are from industrial effluents and from oil spills. The final effluents of sewage treatment plants receiving discharges from these industrial facilities have been noted to have up to 22 µg/l naphthalene, while natural waters have up to 2.0 µg/l, and drinking water supplies have up to 1.4 µg/l naphthalene (U.S. EPA, Region IV, unpublished data).

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B. Food

The U.S. EPA (1979) has estimated the weighted average bio-concentration factor for naphthalene to be 60 for the edible portions of fish and shellfish consumed by Americans. This estimate was based on octanol/water partition coefficients.

C. Inhalation

In the ambient air, inhalation of naphthalene is negligible with vapor concentrations ranging from 0.00005 to 0.0001 $\mu g/m^3$ and particulate concentrations ranging from 0.000003 to 0.00025 $\mu g/m^3$ (Krstulovic, et al. 1977). Industrial exposure can range from 0.72 $\mu g/m^3$ to 1.1×10^6 $\mu g/m^3$ in the vapor phase (Bjrseth, et al., 1978b; Robbins, 1951) and from 0.09 $\mu g/m^3$ to 4.40 $\mu g/m^3$ in particulates (Bjrseth, 1978a, 1978b). Naphthalene has also been found in cigarette smoke condensate (Akin, et al. 1976).

III. PHARMACOKINETICS

A. Absorption

Little detailed information is available on the absorption of naphthalene in man or animals. Adequate amounts of naphthalene can be absorbed when ingested as a solid, or by inhalation, to cause significant toxicity (U.S. EPA, 1979). Absorption seems to be facilitated if naphthalene is dissolved in oil (Solomon, 1957), and hindered if naphthalene is bound to protein (Sanborn and Malins, 1977).

B. Distribution

Naphthalene distributes widely after absorption. In mallards, the relative distribution of naphthalene was as follows: greatest in skin, followed by liver, brain, blood, muscle, and heart (Lawler, et al. 1978).

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C. Metabolism

Naphthalene is first metabolized by hepatic mixed-function oxidases to an epoxide, which is an obligatory step in the metabolism of naphthalene. Further metabolism can occur leading to the formation of a variety of compounds. Most of these compounds are enzymatically conjugated with glucuronic acid or sulfate. During metabolism a number of highly reactive compounds are formed such as 1,2-dihydroxynaphthalene and 1,2-naphthoquinone (U.S. EPA, 1979).

Naphthalene metabolites undergo further conversions in the eye. This multi-step pathway can lead to the formation of 1,2-naphthaquinone which can irreversibly bind to lens protein and amino acids (Van Heyningen and Pirie, 1966).

D. Excretion

Naphthalene has not been identified in urine after absorption. With sufficient absorption of naphthalene to result in toxicity to an 18 month old infant, Mackell, et al. (1951) noted metabolites of naphthalene in the urine that were still identifiable two weeks after exposure but which had disappeared 18 days after exposure.

1-Napthol is the predominant spontaneous decomposition product of the epoxide of napohthalene. 1-Napthol is excreted unchanged as well as congugated with glucuronic acid or sulfate prior to excretion. The finding of 1,4-nathoquinone in the urine of a child poisoned with naphthalene (Mackell, et al. 1951) suggests that 1-napthol can also be further oxidized in mammals (Cerniglia and Gibson, 1977).

IV. EFFECTS

A. Carcinogenicity

In attempts to demonstrate its carcinogenicity, naphthalene has been given orally, subcutaneously, implanted in the bladder, and painted

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on the backs of a number of animal species (U.S. EPA, 1979). In these experiments naphthalene caused no increase in tumor formation. Two experiments have produced increases in lymphosarcoma and lymphatic leukemia after treatment with coal tar derived naphthalene. The first of these studies (Knake, 1956) was complicated by the presence of 10 percent impurities in the naphthalene and the painting of the injection site with carbolfuchsin, a known experimental carcinogen, prior to injection. In the second study (Knake, 1956) where excess leukemia was noted, naphthalene was dissolved in benzene, a known human leukemogenic agent, and painted on the backs of mice. Benzene treatment resulted in no leukemia. Skin papillomas have been produced on mice following painting with 1,4-naththa-quinone, a metabolite of naphthalene (Takizawa, 1940). Also, Pirie (1968) noted abnormal mitotic figures in metaphase and cell overgrowth in the epithelial cells of the lens of rabbits given 1 g/kg/day of naphthalene by gavage.

B. Mutagenicity

Naphthalene has been found to be nonmutagenic in several microsomal/bacterial assay systems (McCann, et al. 1975; Kraemer, et al. 1974).

C. Teratogenicity

Pertinent data could not be located in the available literature.

D. Other Reproductive Effects

Naphthalene or its metabolites can cross the placenta in sufficient amounts to cause fetal toxicity (Zinkham and Childs, 1958; Anziulewicz, et al. 1959). When a metabolite of naphthalene, 2-naphthol, was administered to pregnant rabbits, their offspring were born with cataracts and evidence of retinal damage (Van der Hoeve, 1913).

E. Toxicity

Oral administration of two percent naphthalene or 2-napthol to rats for at least 60 days resulted in the development of cataracts (Fitzhugh adn Buscckke, 1949). Van Heyningen and Pirie (1976) dosed rabbits daily by gavage with 1000 mg/kg of naphthalene for a maximum of 28 days. Lens changes developed after the first dose, and retinal changes developed after the second dose. Rabbits fed 1000 mg/kg/day developed cataracts between day 3 and 46. Topical application of a 10 percent solution in oil to the eyes of rabbits did not produce cataracts after a period of 50 days. Intraperitoneal injection of 500 mg/kg of naphthalene in an oily solution produced weight loss over a period of 50 days (Ghetti and Mariani, 1956). Hemolytic anemia with associated jaundice and occasionally renal disease from precipitated hemoglobin has been described in newborn infants, children and adults after exposure to naphthalene by ingestion, inhalation, or possibly by skin contact (U.S. EPA, 1979). The extent or duration of exposure was not given. Mahvi, et al. (1977) noted a dose related damage to bronchiolar epithelial cells in mice given intraperintoneal injections of naphthalene in corn oil. Bronchiolar epithelial changes were not noted in two control groups. The authors noted minor bronchiolar epithelial changes in the treated group receiving 67.4 mg/kg of naphthalene. Those mice receiving higher doses (128 and 256 mg/kg of napnthalene) developed reversible necrosis of bronchiolar cells.

F. Other Relevent Information

Alexandrov and Frayssinet (1973) demonstrated that naphthalene administered intraperitoneally to rats could inhibit the mixed-function microsomal oxidase enzyme system, and could also inhibit the induction of these enzymes by 3-methylcholanthrene.

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V. AQUATIC TOXICITY

A. Acute

For the freshwater mosquitofish (Gambusia affinis) a 96-hour static bioassay provided an LC_{50} value of 150,000 µg/l (Wallen, et al. 1957), while the freshwater cladoceran (Daphnia magna) was shown to have an 48-hour LC_{50} value of 8,570 µg/l (U.S. EPA, 1978). Marine organisms tended to be somewhat more sensitive to naphthalene with an 24-hour static LC_{50} value of 2,400 µg/l for the sheepshead minnow (Cyprinodon variegatus). Two 24-hour static LC_{50} values of 2,500, 2,600 were obtained for two species of marine shrimp, (Penaeus aztecus) and (Palaemonetes pugio), respectively (Anderson, et al. 1974). A 96-hour LC_{50} value of 2,350 µg/l was obtained for grass shrimp (Palaemonetes pugio) (Tatem, 1976).

B. Chronic Toxicity

A single embryo-larval test on the fathead minnow (Pimephales promelas) stated that no effects were observed at concentrations as high as 440 µg/l (U.S. EPA, 1978).

Data pertaining to the chronic toxicity of naphthalene for any marine species could not be located in the available literature.

C. Plant Effects

A 48-hour EC_{50} value of 33,000 µg/l for reduced cell numbers has been reported for the freshwater algae (Chlorella vulgaris) exposed to naphthalene. Data pertaining to the effects of naphthalene to marine plants could not be located in the available literature.

D. Residues

Using the octanol/water partition coefficient of 2,300 for naphthalene, a bioconcentration factor for aquatic organisms with an 8 percent lipid content has been estimated as 210. Bioconcentration

factors determined for marine invertebrates ranged from 50 to 60 in the marine copepod Calanus helgolandicus after one day (Harris, et al. 1977a, 1977b) to 5,000 in the copepod Eurytemora affinis, after nine days, (Harris, et al. 1977b) indicating that equilibrium may not occur rapidly. Bioconcentration factors of 32 to 77 after 1 to 24 hours were reported for these 3 species of marine fish and one species of mussel (Lee, et al. 1972a; 1972b).

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibiliity that these criteria will be changed.

A. Human

The Occupational Safety and Health Administration standard for exposure to vapor for a time-weighted industrial exposure is 50 mg/m^3. The American Conference of Governmental Industrial Hygienists (ACGIH. 1971) threshold limit value is 75 mg/m^3, while at present the ACGIH also suggests a maximum 15 minute exposure value of 75 mg/m^3 (ACGIH, 1978). The acceptable daily intake for naphthalene is 448 µg/day for a 70 kg person. The U.S. EPA (1979) draft ambient water criterion for naphthalene is 143 µg/l.

B. Aquatic

Criterion can not be derived for naphthalene for either fresh-water or marine organisms, because of the lack of sufficient toxicological data.

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NAPHTHALENE

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No. 132

1,4-Naphthoquinone

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

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1,4-NAPHTHOQUINONE

SUMMARY

1,4-Naphthoquinone is used as a polymerization regulator and an intermediate. Some data are available which indicate that 1,4-naphthoquinone is biodegradable.

The most consistent findings reported in the literature for health effects of 1,4-naphthoquinone involve hematological changes, irritant and allergenic activity, and inhibition of biochemical oxidation processes. One study found 1,4-naphthoquinone to be oncogenic. Some evidence of inhibition of *in vitro* endocrine function and of nerve activity was reported.

I. INTRODUCTION

1,4-Naphthoquinone (1,4-naphthalenedione; $C_{10}H_6O_2$; molecular weight 158.15) is a solid at room temperature. It occurs as a greenish yellow powder or as yellow triclinic needles. It has a melting point of 123-126°C and begins to sublime at 100°C; its density is 1.422. 1,4-Naphthoquinone is only slightly soluble in water; it is soluble in a variety of organic solvents (Windholz 1976; Hawley 1971).

Current production (including importation) statistics for 1,4-naphthoquinone (CAS No. 130-15-4) listed in the initial TSCA Inventory (U.S. EPA 1979) show that between 1,000,000 and 9,000,000 pounds of this chemical were produced/imported in 1977. *

1,4-Naphthoquinone is used as a polymerization regulator for rubber and polyester resins, in the synthesis of dyes and pharmaceuticals, and as a fungicide and algicide (Hawley 1971).

II. EXPOSURE

A. Environmental Fate

No specific information on the biological, chemical or photochemical transformation of 1,4-naphthoquinone under environmental conditions was identified in the literature. Napthoquinones undergo few substitution

* This production range information does not include any production/importation data claimed as confidential by the person(s) reporting for the TSCA Inventory, nor does it include any information which would compromise Confidential Business Information. The data submitted for the TSCA Inventory, including production range information, are subject to the limitations contained in the Inventory Reporting Regulations (40 CFR 710).

reactions (Thirtle 1965). Like other quinones, 1,4-naphthoquinone can interconvert with its corresponding hydroquinone in an oxidation-reduction system.

Talakin (1964) reported that 1,4-naphthoquinone in river water apparently undergoes slow biochemical oxidation, based on an observed increase in BOD. Verschueren (1977) reports that the BOD_5 is 0.81, using the standard dilution technique with normal sewage as seed material, and that the theoretical oxidation demand is 2.1.

B. Bioconcentration

No information was found on the bioconcentration potential of 1,4-naphthoquinone. Based on its low water solubility and its solubility in organic solvents, 1,4-naphthoquinone could be expected to bioconcentrate to some extent.

C. Environmental Occurrence

No information was found on the presence of 1,4-naphthoquinone in environmental media.

In addition to its potential entry into the environment from its manufacture, processing and uses, 1,4-naphthoquinone may also enter the environment as a degradation product of certain naphthalene derivatives. For example, the U.S. EPA (1975) reported studies showing that the pesticide carbaryl (1-naphthyl-n-methyl-carbamate) undergoes hydrolysis to 1-naphthol, which is then converted by bacteria to 1,4-naphthoquinone and other products.

III. PHARMACOKINETICS

No information was obtained.

IV. HEALTH EFFECTS

A. Carcinogenicity

1,4-Naphthoquinone was found to induce neoplasm when applied dermally to mice for 28 weeks. The total dose applied was 2000 mg/kg. (Proceedings of the Imperial Academy of Tokyo 16:309, 1940, as cited in NIOSH 1975).

B. Reproductive Effects

1,4-Naphthoquinone completely inhibited the gametokinetic effect of human chorionic gonadotropin in toads (Pakrashi 1963).

C. Other Toxicity

The oral LD_{50} for rats was reported as 190 mg/kg (NIOSH, 1975). The LD_{100} of 1,4-naphthoquinone in rats was 0.5 g/kg, 0.25 g/kg, and 0.5 g/kg for intraventricular, subcutaneous, and intraperitoneal administrations, respectively. The LC_{100} in air was 0.45 mg/L for a one-hour exposure. Acute (0.5 g/kg) and subchronic (0.3 g/kg for 4 days) exposure of rats resulted in the formation of 39 and 18% methemoglobin, respectively, followed by the appearance of Heinz bodies and development of hemolytic anemia. A decrease in total respiration and hypothermia due to disturbances in oxidation-reduction processes was also observed. According to the authors, "threshold concentrations of 1,4-naphthoquinone detected for rats and rabbits in single-exposure and chronic experiments were 0.0004 and 0.0007 mg/L with respect to their irritant and toxic effects" (Slyusar et al. 1964).

D. Other Relevant Information

1,4-Naphthoquinone exerted an allergenic effect in guinea pigs (Kryzhanovskaya et al. 1966). A possible role for 1,4-naphthoquinone in drug-induced thrombocytopenia was suggested by Niewig et al. (1973) as 1,4-naphthoquinone was found to be involved in the destruction of normal blood platelets by serum antibodies in vitro. 1,4-Naphthoquinone blocks the biosynthesis of adrenal steroids by bovine adrenal cortex in vitro (Kahnt and Neher 1966), and has an inhibitory effect on mixtures of cytochrome c and dehydrated succinate oxidase from beef heart (Heymann and Feiser 1966). 1,4-Naphthoquinone inhibited ATPase and nerve activity in the (American) cockroach (Baker and Norris 1971, Baker 1972).

V. AQUATIC TOXICITY

Very little information was available. For 1,4-naphthoquinone, a median threshold limit value (TLM:24-28 hr) of 0.3-0.6 mg/L was listed for an unspecified species of fish (Verschueren 1977).

VI. GUIDELINES

No guidelines for exposure to 1,4-naphthoquinone were located.

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No. 133

Nickel

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated nickel and has found sufficient evidence to indicate that this compound is carcinogenic.

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NICKEL

Summary

Nickel is a ubiquitous multi-media environmental contaminant. Although nickel is toxic and appears to be a carcinogen to man, there is an increasingly strong indication that nickel is an essential element. The route of exposure to nickel is very important, since oral intake of nickel metal is comparatively nontoxic. However, exposure to nickel by inhalation or parenteral administration as well as cutaneous contact can produce toxic effects. In terms of human health effects, probably the most acutely toxic nickel compound is nickel carbonyl. Nickel in several chemical forms has been associated with lung cancer in man and experimental animals upon inhalation; carcinogenic effects, however, are not indicated by the oral route. The acceptable daily intake (ADI) of nickel is 294 µg per day for a 70 kg man.

The toxicity of nickel to aquatic life is affected by water hardness. In the aquatic environment nickel is acutely toxic to freshwater fishes at a concentration of 2,480 µg/l (26 mg/l hardness). Chronic toxicity to fishes has been reported at 527 µg/l (210 mg/l hardness). Nickel toxicity is affected by water hardness. Algae appears to be more sensitive to nickel than fish. Based on the limited number of studies performed, the bioconcentration factor for fish is 61, for algae the factor is 9.8, and the weighted average bioconcentration factor is 11 for fish and shellfish.

NICKEL

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Nickel (U.S. EPA, 1979).

Nickel (Ni; atomic weight 58.71), a bright, silver metal of the iron-cobalt-nickel triad, is a hard and malleable metal with a high tensile strength used in virtually all areas of metallurgy. Nickel does not readily form chloro-complexes under environmental conditions and would not be expected to form significant amounts of sulfate complexes (U.S. EPA, 1979).

In 1972, U.S. consumption of nickel, exclusive of scrap, was estimated to total about 160,000 tons (Reno, 1974). The estimate consisted mainly of commercially pure nickel (about 110,000 tons) which is used in stainless steel, electroplating, and various other alloys.

II. EXPOSURE

The route by which most people in the general population receive the largest portion of daily nickel intake is through foods. Total daily dietary intake values may range up to 900 µg nickel, depending on the nature of the diet, with average values of 300 to 500 µg daily (NAS, 1975). The U.S. EPA (1979) has estimated a weighted average bioconcentration factor for nickel to be 11 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on measured steady-state bioconcentration studies in fathead minnow larvae (Pimephales promelas) (Lind, et al. Manuscript). The values for nickel levels in 969 U.S. public water supplies for 1969-1970 was 4.8 µg/l, with only 11 systems of this total exceeding 25 µg/l (NAS, 1975). The levels of nickel in the air are also low, with a 1974 arithmetic mean level for urban air of 9 ng/m^3 (U.S. EPA, 1976).

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III. PHARMACOKINETICS

A. Absorption

The major routes of nickel absorption are inhalation and ingestion via the diet. Percutaneous absorption is a less significant factor for nickel's systemic effects but important in the allergenic responses to nickel. Collectively the data of Tedeschi and Sunderman (1957), Perry and Perry (1959), Nomoto and Sunderman (1970), Nodiya (1972), and Horak and Sunderman (1973) indicate that 1 to 10 percent of dietary nickel is absorbed. Skin penetration of nickel has been demonstrated with nickel entering at sweat-duct and hair-follicle ostia (Wells, 1956). The extent to which nickel enters the bloodstream by way of the skin cannot be stated at the present time (U.S. EPA, 1979).

Respiratory absorption of various forms of nickel is probably the major route of nickel entry into man under conditions of occupational exposure. Pulmonary absorption into the bloodstream is probably greatest for nickel carbonyl vapor, with animal studies suggesting that as much as half of the inhaled amount is absorbed (Sunderman and Selin, 1968). Nickel in particulate matter is absorbed from the pulmonary tract to a lesser degree than nickel carbonyl (Leslie, et al. 1976). Based on animal studies, nickel appears to have a half-life of several days in the body, yet there is little evidence for tissue accumulation.

B. Distribution

Blood is the main vehicle for transport of absorbed nickel, with serum albumin being the main carrier protein, although a specific nickelrich metalloprotein has been identified in man (NAS, 1975). Tissue distribution of absorbed nickel appears to be dependent on the route of intake. Inhaled nickel carbonyl leads to highest levels in the lung, brain, kidney, liver,

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and adrenals (Armit, 1908; Sunderman and Selin, 1968; Mikheyev, 1971). Parenteral administration of nickel salts usually results in highest levels in the kidney, with significant uptake shown by endocrine glands, liver and lung (Wase, et al. 1954; Smith and Hackley, 1968).

C. Metabolism

A number of disease states and other physiological stresses are reported to alter the movement and tissue distribution of nickel in man as well as experimental animals. In man, increased levels of serum nickel are seen in cases of acute myocardial infarction (D'Alonzo and Pell, 1963; Sunderman, et al. 1972), acute stroke and extensive burn injury (McNeely, et al. 1971). Reduction is seen in hepatic cirrhosis or uremia, possibly secondary to hypoalbuminemia.

Nickel appears to be an essential element, at least in experimental animals. Nickel deficient diets have produced decreased growth rates and impaired reproduction in swine (Anke, et al. 1974) and rats (Schnegg and Kirchgessner, 1975).

D. Excretion

The routes of elimination for nickel in man and animals depend in part on the chemical forms of nickel and the mode of nickel intake. Dietary nickel, due to the low extent of gastrointestinal absorption, is simply lost in the feces (U.S. EPA, 1979). Urinary excretion in man and animals is usually the major clearance route for absorbed nickel. In some instances sweat can constitute a major route of nickel elimination (Hohnadel, et al. 1973). Nodiya (1972) reported a fecal excretion average of 258 µg in Russian students. Horak and Sunderman (1973) determined fecal excretion of nickel in 10 healthy subjects and arrived at a value identical to that found in the Russian study.

IV. EFFECTS

A. Carcinogenicity

A carcinogenic response to various nickel compounds upon injection has been observed in a number of animal studies (Lau, et al. 1972; Stoner, et al. 1976; IARC, 1976). In nickel refinery workers, an excess risk of nasal and lung cancer has been demonstrated (IARC, 1976). However, there is no evidence at present to indicate that orally ingested nickel is tumorigenic.

The qualitative and quantitative character of the carcinogenic effects of nickel as seen in experimental animal models has been shown to vary with the chemical form of the nickel, the route of exposure, the animal model employed, and the amounts of the substance administered (U.S. EPA, 1979).

B. Mutagenicity

Pertinent information could not be located in the available literature.

C. Teratogenicity

While Ferm (1972) has claimed unspecified malformations in surviving hamster embryos when mothers were exposed to parenteral nickel (0.7 to 10.0 mg/kg), Sunderman, et al. (1978) found no teratogenic effects from oral administration of either nickel chloride (16 mg/kg) or nickel subsulfide (80 mg/kg) in rats. Exposure of pregnant rats by inhalation to nickel carbonyl on days 7 or 8 of gestation frequently caused the progeny to develop ocular anomalies, including anophthalmia and microphthalmia. The incidence of extraocular anomalies is very low. The specificity of nickel carbonyl for induction of ocular anomalies in rats appears to be unique among known teratogenic agents (Sunderman, et al. 1979).

D. Other Reproductive Effects

Schroeder and Mitchner (1971) have demonstrated adverse affects in a three generation study with rats at a level of 5 mg/l (5 ppm) nickel in drinking water. In each of the generations, increased numbers of runts and enhanced neonatal mortality were seen. A significant reduction in litter size and a reduced proportion of males in the third generation were also observed. Nickel sulfate (25 mg/kg) has been demonstrated to be gametotoxic in rats, with complete obliteration of spermatozoa following exposure for 120 days (Hoey, 1966; Waltschewa, et al. 1972).

E. Chronic Toxicity

Chronic exposure to nickel has resulted in injury to both the upper and lower respiratory tract in man (Tolot, et al. 1956; McConnell, et al. 1973). Inhalation of nickel particulate matter is likely to play a role in chronic respiratory infections by effects on alveolar macrophages. Contact dermatitis in man with nickel sulfate has been observed (Fregert, et al. 1969; Brun, 1975). Also, dietary nickel can elicit a dermatitic response (Kaaber, et al. 1978).

F. Other Relevant Information

There are experimental data that demonstrate that nickel has a synergistic effect on the carcinogenicities of polycyclic hydrocarbons (Toda, 1962; Maenza, et al. 1971; Kasprzak, et al. 1973). Nickel and other elements are known to be present in asbestos and may possibly be a factor in asbestos carcinogenicity (Cralley, 1971). Also, a synergistic action between nickel and viruses has been suggested (Treagon and Furst, 1970).

V. AQUATIC TOXICITY

A. Acute Toxicity

Water hardness significantly influences the acute toxicity of nickel to freshwater fish. For fish, observed LC_{50} values range from 2,480

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µg/l for the rock bass (Ambloplites rupestris) (hardness = 26 mg/l) to 110,385 µg/l for the bluegill (Lepomis macrochirus) (hardness = 42 mg/l). At a hardness of 20-29 mg/l, six freshwater species have LC_{50} values of between 2,916 and 5,360 µg/l (Pickering and Henderson, 1966; Lind et al., manuscript). At a hardness of 360 µg/l, values range from 39,600 to 44,500 µg/l. In comparison, acute tests with freshwater invertebrate species have a greater range of LC_{50} values at a fixed hardness. The stonefly (Acroneuria lycorias) exhibited the highest LC_{50} of 33,500 µg/l (Warnick and Bell, 1969) and Daphnia magna gave the lowest value of 510 µg/l (Biesinger and Christensen, 1972). Lind, et al. (1979) provide the only data obtained under relatively high hardness conditions (244 mg/l), an LC_{50} value of 2409 µg/l for Daphnia pulicaria.

Data on the acute toxicity of nickel to saltwater fishes is limited. The LC_{50} values range from 29,000 µg/l for the Atlantic Silverside (Menidia menidia) to 350,000 µg/l for the mummichog (Fundulus heteroclitus) (Eisler and Hennekey, 1977). The invertebrate acute toxicity data base consists of 14 results, with a range of LC_{50} values from 310 µg/l for larvae of the hard clam (Mercenaria mercenaria) (Calabrese and Nelson, 1974) to 500,000 µg/l for adults of the cockle Cardium edule (Portmann, 1968).

B. Chronic Toxicity

A life cycle test (Pickering, 1974) and an embryo-larval test (Lind, et al., manuscript) have been conducted with the fathead minnow (Pimephales promelas). The chronic values are 527 µg/l (210 mg/l hardness) and 109 µg/l (44 mg/l hardness) respectively. Biesinger and Christensen (1972) conducted a life cycle test with Daphnia magna resulting in a chronic value of 53 µg/l at a hardness of 45 mg/l. There are no chronic saltwater data available (U.S. EPA, 1979).

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C. Plant Effects

Hutchinson (1973) and Hutchinson and Stokes (1975) observed reduced growth of several algae species at concentrations ranging from 100 to 700 µg/l. A decrease in diatom diversity was observed by Patrick, et al. (1975) to occur at concentrations as low as 2 µg/l.

D. Residues

Bioconcentration data is limited to the fathead minnow, Pimephales promelas, (Lind, et al., manuscript) and the alga, Scenedesmes acuminata (Hutchinson and Stokes, 1975). The bioconcentration factor for the whole body of the fathead minnow is 61 and for the alga the factor is 9.8.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

The American Conference of Governmental Industrial Hygienists (ACGIH, 1971) has adopted a threshold limit value (TLV) for a workday exposure of 1 ppb. The acceptable daily intake (ADI) for man has been determined to be 294 µg/day (U.S. EPA, 1979). The U.S. EPA (1979) draft water quality criterion for nickel is 133 µg/l.

B. Aquatic

For nickel, the draft criterion (U.S. EPA, 1979) to protect freshwater aquatic life is:

$$e^{(1.01 \cdot \ln(\text{hardness}) - 1.02)}$$

as a 24-hour average, and the concentration should not exceed at any time:

$$e^{(0.47 \cdot \ln(\text{hardness}) + 4.19)}$$

The draft criterion to protect saltwater aquatic life is 220 µg/l as a 24-hour average, not to exceed 510 µg/l at any time (U.S. EPA, 1979).

NICKEL

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No. 134

Nitrobenzene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

NITROBENZENE

Summary

Nitrobenzene is a pale yellow oily liquid with an almond-like odor. There is little or no information available on its teratogenic, mutagenic or carcinogenic effects. Nitrobenzene yielded negative results in the Ames assay for mutagenicity. Gross abnormalities were observed in 4 fetuses of 30 rats administered nitrobenzene.

Chronic exposure to nitrobenzene produces cyanosis, methemoglobinemia, jaundice, anemia, and sulfhemoglobinemia in man.

Static tests with the bluegill, sunfish, Daphnia magna, and an alga, Selenestrum capricornutum, indicates little difference in sensitivity with no 50 percent effective concentration lower than 27,000 ug/l. An embryo-larval test with the fathead minnow demonstrated no adverse chronic effects at the highest concentration tested (32,000 µg/l). Static tests with salt-water fish, shrimp, and alga gave repeated 96-hour LC_{50} or EC_{50} values of 58,538 µg/l, 6,676 µg/l and 9,600 µg/l, respectively.

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I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Nitrobenzene (U.S. EPA, 1979). The principal uses of nitrobenzene are for reduction to aniline (97 percent), solvent for Friedel-Crafts reaction, metal polishes, shoe black, perfume, dye intermediates, crystallizing solvent for some substances, and as a combustible propellant (Dorigan and Hushon, 1976).

Nitrobenzene ($C_6H_5NO_2$) is a pale yellow oily liquid with an almond-like odor. Its physical properties include: melting point, 6°C; vapor pressure, 0.340 mm Hg at 25°C; and solubility in water of 1000 mg/l at 20°C (U.S. EPA, 1979). Nitrobenzene is miscible with most organic solvents, a fairly strong oxidizing agent, and undergoes photoreduction when irradiated with ultraviolet light in organic solvents that contain abstractable hydrogen atoms.

II. EXPOSURE

A. Water

Levels of nitrobenzene in wastewater are monitored by plants producing and using the chemical, but nitrobenzene levels in city water systems are usually too low to measure (Pierce, 1979).

B. Food

Nitrobenzene is not an approved food additive (Dorigan and Hushon, 1976). There have been reports of nitrobenzene poisoning resulting from its contamination of alcoholic drinks and food (Nabarro, 1948).

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for nitrobenzene to be 4.3 for the edible portions of fish and shellfish consumed by Americans. This estimate was based on octanol/water partition coefficients.

C. Inhalation

Atmospheric nitrobenzene levels outside a plant are not monitored by industry. Since inner plant levels are below the Threshold Limit Value (TLV) of 5 mg/m^3 and nitrobenzene vapors accumulate at the floor level due to their high density, the external concentrations are expected to be very low (Dorigan and Hushon, 1976).

III. PHARMACOKINETICS

A. Absorption

Nitrobenzene absorption can occur by all possible routes, but it takes place mainly through the respiratory tract and skin. On the average, 80 percent of the nitrobenzene vapors are retained in the human respiratory tract (Piotrowski, 1977).

Nitrobenzene, as liquid and vapor, will pass directly through the skin. The rate of vapor absorption depends on the air concentration, ranging from 1 mg/hr at 5 mg/m^3 concentration to 9 mg/hr at 20 mg/m^3. Maximal cutaneous absorption of liquid nitrobenzene is 0.2 to 3 $mg/cm^2/hr$ depending on skin temperature.

B. Distribution

Upon entry into the body, nitrobenzene enters the bloodstream. Nitrobenzene is a very lipid soluble with an oil to water coefficient of 800. In a rat study, the ratio of concentration of nitrobenzene in adipose tissue versus blood in internal organs and muscle was approximately 10:1 one hour after an intravenous injection (Piotrowski, 1977). Dorigan and Hushon (1976) found that 50 percent of the nitrobenzene administered to rabbits accumulated unchanged in tissues within two days after intubation.

C. Metabolism

There are two main pathways for the metabolism of nitrobenzene: 1) reduction to aniline followed by hydroxylation to aminophenols, and 2) direct hydroxylation of nitrobenzene to form nitrophenols. Further reduction of nitrophenols to aminophenols may also occur (Piotrowski, 1977). The first pathway proceeds via the unstable intermediates, nitrosobenzene and phenylhydroxylamine, both of which are toxic and have pronounced methemoglobinemic capacity. These reactions occur in the cytoplasmic and microsomal fractions of liver cells by the nitro-reductase enzyme system (Fouts and Brodie, 1957). The aniline is then excreted as an acetyl derivative, or hydroxylated and excreted as an aminophenol. The second pathway does not occur in the microsomal fraction. This reaction proceeds via peroxidase in the presence of oxygen (Piotrowski, 1977).

Robinson, et al. (1951) found p-aminophenol to be the main metabolic product of nitrobenzene metabolism in rabbits. Little unchanged nitrobenzene was excreted in the urine and only 1 percent was expired as carbon dioxide. Together with nitrophenols and nitrocatechol, p-aminophenol constituted 55 percent of the urinary metabolites. Metabolites were detected in the urine up to one week after dosing.

D. Excretion

In man, the primary known excretion products of nitrobenzene are p-aminophenol and p-nitrophenol which appear in the urine after chronic or acute exposure. In experimental inhalation exposure to nitrobenzene, p-nitrophenol was formed with the efficiency of 6 to 21 percent. The efficiency of p-aminophenol formation is estimated from acute poisoning

cases where the molar ratio of excreted p-nitrophenol to p-aminophenol is two to one, since p-aminophenol is not formed at a detectable level in short subacute exposure (Piotrowski, 1977).

Ikeda and Kita (1964) found the rate of excretion of these two metabolites to parallel the level of methemoglobin in the blood.

Nitrobenzene remains in the human body for a prolonged period of time. The excretion coefficient of urinary p-nitrophenol (followed for three weeks) in man is about 0.008 per hour. The extended systemic retention and slow excretion of metabolites in man is determined by the low rates of metabolic transformation (reduction and hydroxylation) of the nitrobenzene itself. The conjugation and excretion of the metabolites, p-nitrophenol and p-aminophenol, is rapid (Piotrowski, 1977). The urinary metabolites in man account for only 20 to 30 percent of the nitrobenzene dose; the fate of the rest of the metabolites is not known (Piotrowski, 1977).

IV. EFFECTS

A. Carcinogenicity

The available literature does not demonstrate the carcinogenicity of nitrobenzene, although it is suspect (Dorigan and Hushon, 1976).

Some nitrobenzene derivatives have demonstrated carcinogenic capacities. Pentachloronitrobenzene (PCNB) induced hepatomas and papillomas in mice (Courtney, et al. 1976).

1-Fluoro-2,4-dinitrobenzene (DNFB) was found to be a promoter of skin tumors in mice, although it does not induce them when administered alone (Boch, et al 1969).

B. Teratogenicity

There is a paucity of information on the teratogenic effects of nitrobenzene. In one study, 125 mg/kg was administered to pregnant rats

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during preimplantation and placentation periods (Kazanina, 1968). Delay of embryogensis, alteration of normal placentation, and abnormalities in the fetuses were observed. Gross morphogenic defects were seen in 4 of 30 fetuses examined.

C. Mutagenicity

Nitrobenzene was not found to be mutagenic in the Ames Salmonella assay (Chiu, et al., 1978). Trinitrobenzene and other nitrobenzene derivatives have demonstrated mutagenicity in the Ames Salmonella microsome assay and the mitotic recombination assay in yeast (Simmon, et al. 1977), thus raising questions concerning the mutagenicity of nitrobenzene.

D. Other Reproductive Effects

Changes in the tissues of the chorion and placenta of pregnant women who worked in the production of a rubber catalyst that used nitrobenzene were observed. No mention was made of the effects on fetal development or viability (Dorigan and Husnon, 1976). Menstrual disturbances after chronic nitrobenzene exposure have been reported.

Garg, et al. (1976) tested substituted nitrobenzene derivatives for their ability to inhibit pregnancy in albino rats. Two of the compounds tested (p-methoxy and p-ethoxy derivatives) inhibited implantation and pregnancy 100 percent when administered on days 1 through 7 after impregnation.

E. Chronic Toxicity

Symptoms of chronic occupational nitrobenzene absorption are cyanosis, methemoglobinemia, jaundice, anemia, sulfhemoglobinemia, presence of Heinz bodies in the erythrocytes, dark colored urine, and the presence of nitrobenzene metabolites (e.g., nitrophenol) in the urine (Pacseri and Magos, 1958; Hamilton, 1919; Wuertz, et al. 1964; Browning, 1950; Malden, 1907; Piotrowski, 1967).

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Chronic exposure of laboratory animals to nitrobenzene (via inhalation, ingestion or subcutaneous injection) produced symptoms similar to those mentioned above for humans as well as tissue degeneration of the heart, liver, and kidney, and reductions in erythrocytes and hemoglobin levels in the blood (U.S. EPA, 1979).

F. Other Relevant Information

Alcohol ingestion has been found to act synergistically with nitrobenzene in man and animals (Dorigan and Hushon, 1976; Smyth, et al., 1969).

Kaplan, et al. (1974) showed that caffeine, an inducer of microsomal enzymes, increases the rate of metabolism and excretion of nitrobenzene thus causing a rapid decline in nitrobenzene induced methemoglobin levels.

Metabolism and excretion of nitrobenzene in humans is slower by an order of magnitude than in rats or rabbits (Piotrowski, 1977).

V. AQUATIC TOXICITY

A. Acute Toxicity

The 96-hour LC_{50} reported value for the bluegill (Lepomis macrochirus) is 42,600 µg/l and the observed 48-hour LC_{50} for Daphnia magna is 27,000 µg/l. Saltwater species tested are the sheepshead minnow, Cyprinodon variegatus, which has a reported 96-hour LC_{50} of 58,539 µg/l and the mysid shrimp, Mysidopsis bahia, with a reported 96-hour LC_{50} of 6,676 µg/l (U.S. EPA, 1979).

B. Chronic Toxicity

In the only chronic data available, no adverse effects were observed during an embryo-larval test with the fathead minnow (Pimephales promelas) at nitrobenzene test concentrations as high as 32,000 µg/l (U.S. EPA, 1978).

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C. Plant Effect

Based on cell numbers and chlorophyll a concentration, reported EC_{50} values for the freshwater alga, Selenastrum capricornutum, are 42,000 and 44,100 µg/l; and for the marine alga, Skeletonema costatum, there are reported EC_{50} values of 9,600 and 10,300 µg/l (U.S. EPA, 1979).

D. Residues

A bioconcentration factor of 15 was estimated for aquatic organisms that contain 8 percent lipids.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

The TLV for nitrobenzene is 5 mg/m^3. This is the OSHA Federal standard, the value set by the ILO/WHO committee on Occupational Health, and the TLV suggested by the American Conference of Governmental and Industrial Hygienists (Goldstein, 1975, ACGIH, 1977).

The draft water quality criteria for nitrobenzene is 30 µg/l (U.S. EPA, 1979). This value is based on the TLV and organoleptic level (minimum detectable odor limit in water) of nitrobenzene.

B. Aquatic

For nitrobenzene the drafted criterion to protect freshwater aquatic life is 480 µg/l as a 24-hour average concentration not to exceed 1,100 µg/l at any time. To protect saltwater aquatic life, the 24-hour average is 53 µg/l and this concentration should not exceed 120 µg/l at any time (U.S. EPA, 1979).

NITROBENZENE

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No. 135

4-Nitrophenol

Health and Environmental Effects

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4-NITROPHENOL

SUMMARY

There is no evidence to indicate that 4-nitrophenol is carcinogenic.

Weak mutagenic effects in Saccharomyces and in Proteus have been observed. Results from the Ames assay, the E. coli, and the dominant lethal assay failed to show mutagenic effects from 4-nitrophenol.

No information on the teratogenic or adverse reproductive effects of 4-nitrophenol is available.

A single animal study indicates cumulative chronic toxicity; the methodology of this study was not available for review.

For freshwater organisms, acute values for the toxic effects of 4-nitrophenol ranged from 8,280 to 60,500 µg/l, and 7,170 to 27,100 µg/l for marine organisms. Effective concentrations for aquatic plants fall within these ranges of concentrations.

4-NITROPHENOL

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Nitrophenols (U.S. EPA, 1979).

The mononitrophenols are a family of compounds composed of the isomers resulting from nitro group substitution at the 2,3, and 4 position of phenol (the ortho, meta, and para isomers, respectively). The para isomer, 4-nitrophenol, has a molecular weight of 139.11, a boiling point of 279°C, a melting point of 113-114°C, a density of 1.479 g/ml; it is soluble in water (U.S. EPA, 1979).

Uses of the mononitrophenols include the following: production of dyes, pigments, pharmaceuticals, rubber chemicals, lumber preservatives, photographic chemicals, and pesticidal and fungicidal agents (U.S. EPA, 1979). Production was 17.5 x 10^3 tons per year in 1976 (Chem. Market. Reporter, 1976).

The nitrophenols may be formed via microbial degradation or photodegradation of pesticides (e.g., parathion) containing the nitrophenol moiety. 4-Nitrophenol may be produced in the atmosphere through the photochemical reaction between benzene and nitrogen monoxide (U.S. EPA, 1979). Partial microbial degradation of certain nitrophenols has been shown, particularly by acclimated microorganisms. Mononitrophenols appear to be efficiently degraded by unacclimated microorganisms (Haller, 1978).

II. EXPOSURE

The lack of monitoring data on the mononitrophenols makes it difficult to assess exposure from water, inhalation, and foods.

Mononitrophenols in water have been detected in the effluents of chemical plants (U.S. EPA, 1976, 1979). 4-Nitrophenol has been shown to penetrate the skin and to produce damage at threshold concentrations of 0.8 and 0.9 percent %(w/v), respectively (U.S. EPA, 1979).

Exposure to nitrophenols appears to be primarily through occupational contact (chemical plants, pesticide applications). Contaminated water may result in isolated poisoning incidents.

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for 4-nitrophenol to be 4.9 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficient.

III. PHARMACOKINETICS

A. Absorption and Distribution

Pertinent data could not be located in the available literature regarding absorption or distribution.

B. Metabolism

Metabolism of the mononitrophenols occurs primarily by conjugation. Other possible routes are reduction of the nitro group to an amino group or oxidation to dihydric-nitrophenols (U.S. EPA, 1979). These reactions are mediated primarily by liver enzyme systems, although other tissues show lower metabolizing activity (U.S. EPA, 1979).

B. Excretion

An animal study has indicated that oral or intraperitoneal administration of 4-nitrophenol leads to rapid elimination in all species tested, and that the total elimination period is not likely to exceed one week (Lawford, et al. 1954).

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IV. EFFECTS

A. Carcinogenicity

There is no evidence available regarding the carcinogenicity of mononitrophenols.

B. Mutagenicity

A weak mutagenic effect was detected in Saccharomyces cerevisiae by 4-nitrophenol (Fahrig, 1974); this was also indicated by testing 4-nitrophenol for growth inhibition in a DNA repair deficient strain of Proteus mirabilis (Adler, et al., 1976). This compound has also induced chromosome breaks in plants (U.S. EPA, 1979). 4-Nitrophenol has failed to show mutagenic effects in the Ames assay, in E. coli, or in the dominant lethal assay (U.S. EPA, 1979).

C. Teratogenicity and Other Reproductive Effects

Pertinent data could not be located in the available literature regarding teratogenicity and other reproductive effects.

D. Chronic Toxicity

A single Russian study (Makhinya, 1969) reported that chronic administration of mononitrophenol to mammals produced hepatitis, splenic hyperplasia, and neurological symptoms. Methodology of this study was not available for review.

V. AQUATIC TOXICITY

A. Acute Toxicity

LC_{50} values have been obtained for two species of freshwater fish: 8,280 µg/l for bluegills, Lepomis macrochirus, in a 96-hour static assay (U.S. EPA, 1978), and 60,510 µg/l for the fathead minnow, Pimephales promelas, in a 96-hour flow-through assay (Phipps, et al. unpublished manuscript). For the fresh-

water invertebrate, Daphnia magna, determined LC_{50} values range from 8,396 to 21,900 µg/l (U.S. EPA, 1979). The marine fish, sheepshead minnow, Cyprinodon variegatus, has produced determined LC_{50} value of 27,100 816 µg/l in a 96-hour static assay, while the marine mysid shrimp, Mysidopis bahia, was more sensitive, with a reported LC_{50} value of 7,170 µg/l.

B. Chronic Toxicity

No chronic studies on freshwater organisms are available. In an embryo-larval test of the marine fish, sheepshead minnow, a chronic value of 6,325 µg/l was obtained. No chronic testing for marine invertebrates was available.

C. Plant Effects

Four species of freshwater plants have been tested with 4-nitrophenol. The algae, Selenastrum capricornutum and Chlorella vulgaris, and the duckweed, Lemna minor, were most sensitive with effective concentrations of 4,190, 6,950, and 9,452 µg/l, respectively; while the alga, Chlorella pyrenoidosa, was much more resistant, with an effective concentration of 25,000 µg/l. The marine alga, Skeletonema costatum, provided effective concentrations of 7,370 to 7,570 µg/l (U.S. EPA, 1979).

D. Residues

No bioconcentration factors for either fresnwater or marine species were available.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of review; therefore, there is a possibility that these criteria will be changed.

A. Human

Available data pertaining to 4-nitrophenol is insufficient for deriving a criterion to protect human health.

B. Aquatic

A criterion for protecting freshwater organisms has been drafted as 240 µg/l, for a 24-hour average concentration, not to exceed 550 µg/l. For marine life, a criterion has been drafted as 53 µg/l for a 24-hour average, not to exceed 120 µg/l (U.S. EPA, 1979).

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No. 136

Nitrophenols

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NITROPHENOLS

SUMMARY

None of the nitrophenols have shown carcinogenic activity.

Mutagenicity testing has indicated positive effects of: 2,4-dinitrophenol in mouse bone marrow cells and E. coli; 2,4,6-trinitrophenol in E. coli and Salmonella; and 4,6-dinitro-ortho-cresol in Proteus. Weak mutagenic effects of 4-nitrophenol have been reported in Saccharomyces and in Proteus. Other mutagenic test assays have shown negative results for these compounds.

Teratogenic effects have been reported in the developing chick embryo following administration of 2,4-dinitrophenol. This compound did not produce teratogenic effects in mammalian studies. Adverse reproductive effects (embryo toxicity) were seen in rats exposed to 2,4-dinitrophenol.

The chronic effects of 2,4-dinitrophenol ingestion have included cases of agranulocytosis, neuritis, functional heart damage, and cataract formation. Ingestion of 4,6-dinitro-ortho-cresol has also produced cataracts in humans.

One Russian study has reported cumulative toxic effects in animals produced by the mononitrophenols; methodology of this study was not available for review.

Freshwater fish appeared to be the most sensitive organism to the action of nitrophenols, with acute values ranging from 230 to 167,000 µg/l. The reactivities of various nitrophenols in order of decreasing toxicity are, in general: 2,4-dinitro-6-methylphenol, 2,4-dinitrophenol, 2-nitrophenol, 4-nitrophenol, and 2,4,6-trinitrophenol.

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NITROPHENOLS

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Nitrophenols (U.S. EPA, 1979).

The nitrophenols are a family of compounds which, depending on the extent and position of nitro group substituents, include the mononitrophenols, dinitrophenols, and trinitrophenols. Dinitrocresols are related compounds bearing an additional 2-position methyl group. The mononitrophenols (molecular weight 139.11) show boiling points from 194-279°C (depending on the isomeric form) and melting points of 44-114°C. They have a density of 1.485 and are soluble in water. The dinitrophenols (molecular weight 184.11) have melting points from 63.5-144°C and show a density of 1.67 to 1.70. Water solubility is from 0.42 to 2.3 g/l. Trinitrophenols (molecular weight 229.11) have melting points from 96-123°C; they are slightly soluble in water. 2,4,6-Trinitrophenol, the most widely used isomer, has a density of 1.763 g/ml and a solubility of 1.28 g/l. Of the six isomers of dinitrocresol, 4,6-dinitro-o-cresol is the only one of any commercial importance. The physical properties of 4,6-dinitro-o-cresol, hereafter referred to as dinitro-ortho-cresol, include a molecular weight of 198.13, a melting point of 85.8°C and a solubility of 100 mg/l in water (U.S. EPA, 1979).

Uses of the mononitrophenols include the following: production of dyes, pigments, pharmaceuticals, rubber chemi-

cals, lumber preservatives, photographic chemicals, and pesticidal and fungicidal agents. The dinitrophenols are used as chemical intermediates for sulfur dyes, azo dyes, photochemicals, pest control agents, wood preservatives, and explosives. 2,4,6-Trinitrophenol (picric acid) is used for dye intermediates, germicides, tanning agents, fungicides, tissue fixative, photochemicals, pharmaceuticals, and for the etching of metal surfaces. Dinitro-ortho-cresol is used primarily as a blossom-thinning agent on fruit trees and as a fungicide, insecticide, and miticide on fruit trees during the dormant season (U.S. EPA, 1979).

Current Production:	2-nitrophehol	5- 7.5×10^3	tons/year (1976)
	4-nitrophenol	17.5×10^3	tons/year (1976)
	2,4-dinitrophenol	4.3×10^2	tons/year (1968)

The nitrophenols may be formed via microbial degradation or photodegradation of pesticides (e.g., parathion) containing the nitrophenol moiety (U.S. EPA, 1979). Partial microbial degradation of certain nitrophenols has been shown, particularly by acclimated microorganisms. Mononitrophenols appear to be efficiently degraded by unacclimated microorganisms (Haller, 1978).

II. EXPOSURE

The lack of monitoring data on the nitrophenols makes it difficult to assess exposure from water, inhalation, and foods. Nitrophenols in water have been detected in

effluents from chemical plants (U.S. EPA, 1976; 1979) or following dumping of explosives (Harris, et al. 1946). Dermal absorption of mononitrophenols, dinitrophenols, trinitrophenols (picric acid), and dinitro-ortho-cresol (DNOC) has been detected (U.S. EPA, 1979).

Exposure to nitrophenols appears to be primarily through occupational contact (chemical plants, pesticide application). Contaminated water may result in isolated poisoning incidents.

The U.S. EPA (1979) has estimated weighted average bioconcentration factors for the following nitrophenols: 2-nitrophenol, 4.0; 4-nitrophenol, 4.9; 2,4-dinitrophenol, 2.4; 2,4,6-trinitrophenol, 6.0; and 4,6-dinitrocresol, 7.5 for fish and shellfish consumed by Americans. This estimate is based on octanol/water partition coefficients.

III. PHARMACOKINETICS

A. Absorption

Specific data on the absorption of the mononitrophenols is not available. The dinitrophenols are readily absorbed following oral, inhalation, or dermal administration. Data on the absorption of trinitrophenols is not available. Animal studies with oral administration of 2,4,6-trinitrophenol indicate that it is readily absorbed from the gastrointestinal tract. Dinitro-ortho-cresol is readily absorbed through the skin, the respiratory tract, and the gastrointestinal tract in humans (NIOSH, 1978).

B. Distribution

No information on the distribution of the mono-nitrophenols is available. Dinitrophenol blood levels rise rapidly after absorption, with little subsequent distribution or storage at tissue sites (U.S. EPA, 1979). 2,4,6-Trinitrophenol and dinitro-ortho-cresol have been found to stain several body tissues; however, the compounds may be bound to serum proteins, thus producing non-specific organ distribution (U.S. EPA, 1979).

C. Metabolism

Metabolism of the nitrophenols occurs through conjugation, reduction of nitro groups to amino groups, or oxidation to dihydric-nitrophenols (U.S. EPA, 1979). These reactions are mediated primarily by liver enzyme systems, although other tissues show lower metabolizing activity (U.S. EPA, 1979). The metabolism of dinitro-ortho-cresol is very slow in man as compared to that observed in animal studies (King and Harvey, 1953).

D. Excretion

Evidence from human poisoning with parathion indicates that excretion of 4-nitrophenol in the urine is quite rapid (Arteberry, et al. 1961). Experiments with urinary clearance of dinitrophenols in several animal species indicate rapid elimination of these compounds (Harvey, 1959). 2,4,6-Trinitrophenol has been detected in the urine of exposed human subjects indicating at least partial urinary elimination (Harris, et al. 1946). The experiments of Parker

and coworkers (1951) in several animal species indicate that dinitro-ortho-cresol is rapidly excreted following injection; however, Harvey, et al. (1951) have shown slow excretion of dinitro-ortho-cresol in human volunteers given the compound orally.

IV. EFFECTS

A. Carcinogenicity

There are no available data to indicate that the mononitrophenols are carcinogenic. Both 2- and 4-nitrophenol failed to show promoting activity for mouse skin tumors (Boutwell and Bosch, 1959); this same study failed to show promoting activity for 2,4-dinitrophenol. No evidence is available to indicate that dinitrophenols, trinitrophenols, or dinitro-ortho-cresol produce any carcinogenic effects (U.S. EPA, 1979).

B. Mutagenicity

A weak mutagenic effect was detected in Saccharomyces cerevisiae for 4-nitrophenol (Fahrig, 1974); this was also indicated by testing 4-nitrophenol for growth inhibition in a DNA repair deficient strain of Proteus mirabilis (Adler, et al. 1976). This compound has also induced chromosome breaks in plants (U.S. EPA, 1979). 4-Nitrophenol has failed to show mutagenic effects in the Ames assay, in E. coli, or in the dominant lethal assay (U.S. EPA, 1979).

Testing of 2,4-dinitrophenol has indicated mutagenic effects in E. coli (Demerec, et al. 1951) and damage in murine bone marrow cells (chromatid breaks) (Mitra and Manna, 1971). In vitro assays of unscheduled DNA synthesis

(Friedman and Staub, 1976) and DNA damage induced during cell culture (Swenberg, et al. 1976) failed to show positive results with this compound.

2,4,6-Trinitrophenol has produced mutations in E. coli and Salmonella assays (Demerec, et al. 1951; Yoshikawa, et al. 1976). Testing in Drosophila has failed to indicate mutagenic activity.

Adler, et al. (1976) have reported that dinitro-ortho-cresol shows some evidence of producing DNA damage in Proteus mirabilis. Testing of this compound in the Ames Salmonella system (Anderson, et al. 1972) or in E. coli (Nagy, et al. 1975) failed to show any mutagenic effects.

C. Teratogenicity

No information is available to indicate that mono-nitrophenols, 2,4,6-trinitrophenol, or dinitro-ortho-cresol produce teratogenic effects.

2,4-Dinitrophenol has produced developmental abnormalities in the chick embryo (Bowman, 1967; Miyamoto, et al. 1975). No teratogenic effects were observed following intragastric administration to rats (Wulff, et al. 1935) or intraperitoneal administration to mice (Gibson, 1973).

D. Other Reproductive Effects

Feeding of 2,4-dinitrophenol to pregnant rats produced an increased mortality in offspring (Wulff, et al. 1935); similarly, intraperitoneal administration of the compound to mice induced embryotoxicity (Gibson, 1973).

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Influence of the compound on maternal health may have contributed to these effects (U.S. EPA, 1979).

E. Chronic Toxicity

Chronic administration of mononitrophenols to mammals has been reported to produce hepatitis, splenic hyperplasia, and neurological symptoms in a single Russian study (Makhinya, 1969). Methodology of this study was not available for review.

Use of 2,4-dinitrophenol as a human dieting aid has produced some cases of agranulocytosis, neuritis, functional heart damage, and a large number of cases of cataracts (Horner, 1942). Cataracts have also been reported in patients poisoned with dinitro-ortho-cresol (NIOSH, 1978).

Human effects resulting from 2,4,6-trinitrophenol exposure have been reported as temporary impairment of speech, memory, walking, and reflexes (Dennie, et al. 1929).

F. Other Relevant Information

A synergistic action in producing teratogenic effects in the developing chick embryo has been reported with a combination of 2,4-dinitrophenol and insulin (Landauer and Clark, 1964).

The combination of 2,4,6-trinitrophenol and opioids or minor analgesics produced an increase in analgesia (Huidobro, 1971).

2,4-Dinitrophenol is a classical uncoupler of oxidative phosphorylation, which accounts for its marked acute toxicity. Dinitro-ortho-cresol is also well known for its activity as an uncoupler.

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V. AQUATIC TOXICITY

A. Acute Toxicity

Freshwater fish LC_{50} values reported for the bluegill (Lepomis macrochinus) ranged from 230 to 167,000 µg/l and for the juvenile fathead minnow (Pimephales promelas), from 2,040 to 60,510 µg/l. The order of decreasing toxicity for five nitrophenols examined was: 2,4-dinitro-6-methyl phenol, 2,4-dinitrophenol, 2-nitrophenol, 4-nitrophenol, 2,4,6-trinitrophenol (U.S. EPA, 1979). For three of the phenols tested with both the bluegill and fathead minnow, the bluegill appeared more sensitive. In static bioassays with the freshwater invertebrate, Daphnia magna, 48-hour LC_{50} values of 4,090 to 4,710; 8,396 to 21,900; and 84,700 µg/l were reported for 2,4-dinitrophenol, 4-nitrophenol and 2,4,6-trinitrophenol, respectively (U.S. EPA, 1979). The marine fish, sheepshead minnow (Cyprinodon variegatus), was the only fish species acutely tested for three nitrophenols, with reported LC_{50} values of 29,400; 27,100 and 134,000 µg/l being obtained for 2,4-dinitrophenol, 4-nitrophenol, and 2,4,6-trinitrophenol. Observed LC_{50} values of 4,350; 7,170 and 19,700 µg/l were reported for the mysid shrimp (Mysidopsis bahia) for the same three formulations, respectively.

B. Chronic Toxicity

Pertinent information on the chronic effects on freshwater species could not be located in the available literature searches. The only chronic test on a marine

species was an embryo-larval assay of the sheepshead minnow that produced a chronic value of 6,325 µg/l (U.S. EPA, 1978). Pertinent information relative to chronic effects on marine invertebrates could not be located in the available literature.

C. Plant Effects

The effects of various nitrophenols vary widely among species of freshwater plants and according to the formulation of nitrophenol tested. The duckweed, Lemna minor, was the most sensitive plant tested with 2,4-dinitrophenol and was the most resistant with 2-nitrophenol, having effective concentrations (50 percent growth reduction, time unspecified) ranging from 1,472 to 62,550 µg/l for the two respective formulations. The marine alga, Skeletonema costatum, appeared to be slightly more resistant than freshwater species tested, with effective concentrations ranging from 7,370 to 141,000 µg/l for 4-nitrophenol and 2,4,6-trinitrophenol, respectively.

D. Residues

Bioconcentration factors were not determined for any freshwater or marine species. However, based on octanol/water partition coefficients, bioconcentration factors were estimated as 8.1, 21, and 26 for 2,4-dinitrophenol, 2,4,6-trinitrophenol, and 2,4-dinitro-6-dimethylphenol, respectively.

VI. EXISTING GUIDELINES AND STANDARDS

The human health and aquatic criteria derived by U.S. EPA (1979), which are summarized below, have not yet gone through the process of public review; therefore, there is a possibility that these criteria may be changed.

A. Human

Eight-hour TWA exposures for 2,4,6-trinitrophenol (0.1 mg/m^3) and 4,6-dinitro-ortho-cresol (0.2 mg/m^3) have been established by the ACGIH (1971).

Draft water quality criteria for the following nitrophenols have been estimated by U.S. EPA (1979) based on adverse effects data: dinitrophenols - 68.6 µg/l; trinitrophenols - 10 µg/l; and dinitrocresols - 12.8 µg/l.

B. Aquatic

Criteria drafted to protect freshwater life from nitrophenols follow: 57 µg/l as a 24-hour average concentration, not to exceed 130 µg/l, for 2,4-dinitro-6-methylphenol; 79 µg/l, not to exceed 180 µg/l, for 2,4-dinitrophenol; 240 µg/l, not to exceed 550 µg/l, for 4-nitrophenol; 2,700 µg/l, not to exceed 6,200 µg/l, for 2-nitrophenol; and 1,500 µg/l, not to exceed 3,400 µg/l, for 2,4,6-trinitrophenol. For marine life the following criteria have been drafted as 24-hour average concentrations: 37 µg/l, not to exceed 84 µg/l, for 2,4-dinitrophenol; 53 µg/l, not to exceed 120 µg/l, for 4-nitrophenol; and 150 µg/l, not to exceed 340 µg/l, for 2,4,6-trinitrophenol.

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No. 137

Nitrosamines

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated nitrosamines and has found sufficient evidence to indicate that this compound is carcinogenic.

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NITROSAMINES

Summary

Nitrosamines and nitrosamides are widespread in the environment and can also be produced endogenously by nitrosation of constituents of food. Nitrosamines and nitrosamides are considered to be among the most potent of all carcinogenic, mutagenic, and teratogenic agents known. The livers of rats chronically exposed to nitrosamines exhibit pathological changes.

Toxicity data examining the effects of nitrosamines on aquatic organisms is scant. For freshwater life forms, acute toxicity levels of 5,850 to 7,760 µg/l were reported, while for marine fish an acute value of nearly 3,300,000 µg/l was reported (both values for N-nitrosodiphenylamine). N-nitrosodimethylamine has been shown to induce hepatocellular carcinoma in rainbow trout.

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NITROSAMINES

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Nitrosamines (U.S. EPA, 1979).

The nitrosamines (and nitrosamides) belong to a large group of chemicals generally called N-nitroso compounds. Because they frequently coexist with N-nitrosamines in the environment and are structurally related to nitrosamines, nitrosamides are also included in the U.S. EPA (1979) document and in this profile.

The nitrosamines vary widely in their physical properties and may exist as solids, liquids or gases. Nitrosamines of low molecular weight are volatile at room temperature, while those of high molecular weight are steam volatile. Nitrosamines are soluble in water and organic solvents (U.S. EPA, 1976).

Synthetic production of nitrosamines is limited to small quantities. The only nitrosamine produced in quantities greater than 450 kg per year is N-nitrosodiphenylamine, which is used in rubber processing and in the manufacture of pesticides. Other N-nitroso compounds are produced primarily as research chemicals (U.S. EPA, 1976).

Nitrosamines are rapidly decomposed by sunlight and thus do not persist in ambient air or water illuminated by sunlight (U.S. EPA, 1979; Fine, et al. 1977a). Some nitrosamines have been found to persist for extended periods of time in the aquatic environment (Fine, et al. 1977a; Tate and Alexander, 1975).

II. EXPOSURE

Nitrosamines are widespread in the environment. The most probable source of environmental nitrosamines is nitrosation of amine and amide precursors which are ubiquitous in the environment (Bogovski, et al. 1972).

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It has been estimated that air, diet, and smoking all play a roughly equivalent role in human exposure to preformed nitrosamines, contributing a few micrograms per day; intake from drinking water is probably much less than 1 ug per day (U.S. EPA, 1976).

A. Water

Significant concentrations of nitrosamines have been reported for a limited number of samples of ocean water, river water, and waste treatment plant effluent (3 to 4 µg dimethylnitrosamine/l) adjacent to or receiving wastewater from industries using nitrosamines or secondary amines in production operations (Fine, et al. 1977b). Well water with high nitrate levels and coliform counts had nitrosamine concentrations of less than 0.015 µg/l (U.S. EPA, 1977). Non-volatile nitrosamines have been tentatively identified in New Orleans drinking water at levels of 0.1 to 0.5 µg/l (Fine, et al. 1976).

Contamination of water can occur both from industrial wastewater and from agricultural runoff.

B. Food

Nitrosamines have been found in foods, particularly in meats such as sausages, ham, and bacon which have been cured with nitrite. N-nitrosodimethylamine was present in a variety of foods in the 1 to 10 µg/kg range and occasionally at levels up to 100 µg/kg (Montesano and Bartsch, 1976). N-nitrosopyrrolidine has been consistently found in cooked bacon in the range of 10-50 µg/kg (Fine, et al. 1977a).

Many food constituents can either be converted directly to N-nitroso compounds or give rise to nitrosatable products after a metabolic intermediate step which can be involved directly or indirectly in such reactions.

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Constituents include nitrate, nitrite, some amino acids, choline, phospholipids, purines, pyrimidines, some vitamins, caffeine, and some pesticides (Walters, 1977; Elsperu and Lijinsky, 1973).

Nitrate and nitrite are well supplied in the diet. Eighty-six percent of the nitrate ingested comes from vegetables; 9 percent comes from cured meats. Only 2 percent of the nitrite ingested comes from vegetables, while 21 percent comes from cured meat (White, 1975).

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor to be 500 for N-nitrosodiphenylamine in the edible portions of fish and shellfish consumed by Americans. This estimate is based on measured steady-state bioconcentration studies with bluegills. Based on the octanol/water partition coefficient for each compound, the U.S. EPA (1979) has estimated weighted average bioconcentration factors for the following compounds in the edible portions of fish and shellfish consumed by Americans: N-nitrosodimethylamine, 0.06; N-nitrosodiethylamine, 0.39; N-nitroso-di-n-butylamine, 4.9; and N-nitrosopyrrolidine, 0.12.

C. Inhalation

Due to the photolabile nature of nitrosamines, concentrations in ambient air are very low, except near sources of direct emissions of nitrosamines (i.e. chemical plants) (Fine, et al. 1977a). Nitrosamines were detected only twice at 40 collection points in New Jersey and New York City, and then only below the 0.01 $\mu g/m^3$ level.

Tobacco and tobacco smoke contain both secondary amines and nitrosamines (Hoffman, et al. 1974). The intake of nitrosamines from smoking 20 cigarettes per day has been estimated at approximately 6 µg/day (U.S. EPA, 1979).

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III. PHARMACOKINETICS

A. Absorption

Pertinent data could not be located in the available literature.

B. Distribution

Following intravenous injection into rats, nitrosamides and nitrosamines are rapidly and fairly uniformly distributed throughout the body (Magee, 1972; Stewart, et al. 1974). Both nitrosamides and nitrosamines appear to cross the placenta since they induce neoplasms in offspring if administered maternally to rats in late pregnancy (Magee, et al. 1976).

C. Metabolism and Excretion

Nitrosamides are rapidly metabolized in animals and excreted in the urine within 24 hours (Magee, et al. 1976).

Nitrosamines are metabolized less rapidly and persist in the body unchanged for a longer period. The rate of metabolism depends upon the chemical structure (U.S. EPA, 1979).

After administration of ^{14}C-labeled dimethylnitrosamine, diethylnitrosamine, or nitrosomorpholine, the amount of isotope appearing as $^{14}CO_2$ within 12 hours is 60, 45, and 3 percent, respectively, while the corresponding urinary excretions are 4, 14, and 80 percent. Urinary metabolites include other nitroso compounds formed by oxidation of the alkyl groups to the alcohols and carboxylic acids (Magee, et al. 1976). Dimethylnitrosamine is excreted in the milk of female rats (Schoental, et al. 1974).

The liver appears to be the major site for metabolism of nitrosamines; kidney and lung also metabolize nitrosamines (Magee, et al. 1976). The metabolites of nitrosamines are thought to be the active teratogenic, mutagenic and carcinogenic forms (U.S. EPA, 1979).

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IV. EFFECTS

A. Carcinogenicity

The epidemiological studies conducted to date have been inadequate to establish any correlation between exposure to N-nitroso compounds or their precursors and human cancer (U.S. EPA, 1979).

In animals, nitrosamines and nitrosamides are potent carcinogens, inducing tumors in essentially all vital organs via all routes of administration (Montesano and Bartsch, 1976; Druckrey, et al. 1967).

Many of the N-nitroso compounds which have been tested are carcinogenic. There is a strong relationship between chemical structure and type of tumors produced. Symmetrically substituted dialkylnitrosamines and some cyclic nitrosamines produced carcinomas of the liver. Asymmetrical dialkylnitrosamines produced carcinomas of the esophagus (Druckrey, et al. 1967). Apparently all N,N-dialkylnitrosamines containing a tert-butyl group are noncarcinogenic (Heath and Magee, 1962).

There are large differences in species response to carcinogenic nitrosamines and nitrosamides, both in type of tumor produced and in susceptibility, but all animal species tested are vulnerable. The late fetus and neonate appear to be highly susceptible (U.S. EPA, 1979). Exposure to nitrosamides during pregnancy may result in a risk not only to the immediate offspring, but also for at least two more generations of animals (Montesano and Bartsch, 1976). There is no evidence to indicate that nitrosamines pose a similar threat (U.S. EPA, 1979).

Daily oral doses of N-nitroso compounds of 2.5 percent of the LD_{50} values were sufficient to induce cancer in rats (Druckrey, et al. 1967).

B. Mutagenicity

The N-nitroso compounds include some of the most powerful mutagens known. Nitrosamides are mutagenic in almost all test systems, due to non-enzymic formation of active degradation products. Nitrosamines must be metabolically activated to be mutagenic in microbial assays (U.S. EPA, 1979).

Dimethylnitrosamine and diethylnitrosamine have been reported to induce forward and reverse mutations in S. typhimurium, E. coli, Neurospora crassa and other organisms; gene recombination and conversion in Saccharomyces cerevisiae; "recessive lethal mutations" in Drosophila; and chromosome aberrations in mammalian cells (Montesano and Bartsch, 1976). Negative results were obtained in the mouse dominant lethal test.

C. Teratogenicity

N-nitroso compounds can be potent teratogens (U.S. EPA, 1979). Nitrosamides are teratogenic over an extended period of gestation, whereas nitrosamines are active only when administered late in pregnancy (Druckrey, 1973) probably because of the inability of the embryonic tissue to metabolize nitrosamines during early pregnancy (Magee, 1973).

D. Other Reproductive Effects

Nitrosamines and nitrosamides are embryotoxic (Druckrey, 1973).

E. Chronic Toxicity

The livers of rats and other species chronically exposed to nitrosamines exhibit pathological changes including biliary hyperplasia, fibrosis, nodular parenchymal hyperplasia, and the formation of enlarged hepatic parenchymal cells with large nuclei (Magee, et al. 1976).

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F. Other Relevant Information

Unlike nitrosamines, nitrosamides cause tissue injury at the site of contact (Magee, et al. 1976). This is thought to be due to the nonenzymatic decomposition of nitrosamides into active products upon contact with tissues.

Aminoacetonitrile, which inhibits the metabolism of dimethylnitrosamine, prevented the toxic and carcinogenic effects of dimethylnitrosamine in rat liver (Magee, et al. 1976).

Ferric oxide, cigarette smoke, volatile acids, aldehydes, methyl nitrite, and benzo(a)pyrene have been suggested to act in a cocarcinogenic manner with dimethylnitrosamine (Stenback, et al. 1973; Magee, et al. 1976).

V. AQUATIC TOXICITY

A. Acute Toxicity

The LC_{50} value of 5,850 µg/l for bluegill sunfish (Lepomis macrochirus) exposed to N-nitrosodiphenylamine represents the sole acute toxicity data for freshwater fish, while an LC_{50} value of 7,760 µg/l was obtained for the freshwater invertebrate, Daphnia magna (U.S. EPA, 1978). The marine mummichog (Fundulus heteroclitus) was relatively resistant to N-nitrosodimethylamine in a 96-hour static test, where an adjusted LC_{50} value of 3,300,000 µg/l was reported (Ferraro, et al. 1977). No additional data concerning marine organisms was presented in the Ambient Water Quality Criteria Document (U.S. EPA, 1979).

B. Chronic Toxicity

The chronic effects of N-nitrosodiphenyl amine have been examined in Daphnia magna, with no adverse effects being reported at a concentration of 48 µg/l. No chronic data concerning marine organisms were found in the available literature.

C. Plant Effects

Pertinent data could not be located in the available literature.

D. Residues

A bioconcentration factor of 217 was reported, as was a biological half-life of less than one day in the freshwater bluegill sunfish (U.S. EPA, 1978). No data on residues in marine life were found in the available literature.

E. Miscellaneous

Shasta strain rainbow trout (Salmo gairdneri) fed N-nitrosodimethylamine in their diet for 52 weeks developed a dose-response occurrence of hepatocellular carcinoma at doses of 200, 400, and 800 mg N-nitrosodimethylamine per kg body weight (Grieco, et al. 1978).

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

Using the "one-hit" model, the U.S. EPA (1979) has estimated the following levels of nitrosamines in ambient water which will result in specified risk levels of human cancer.

The water concentration of dimethylnitrosamine corresponding to a lifetime cancer risk for humans of 10^{-5} is 0.026 µg/l, based on the induction of liver tumors in rats (Druckrey, 1967).

The water concentration of dibutylnitrosamine corresponding to a lifetime cancer risk for humans of 10^{-5} is 0.013 µg/l, based on induction of tumors of the bladder and esophagus in mice (Bertram and Craig, 1970).

The water concentration of N-nitroso-pyrrolidine corresponding to a lifetime cancer risk for humans of 10^{-5} is 0.11 µg/l, based on the induction of hepatocellular carcinomas in rats (Preussman, et al. 1977).

No other guidelines or standards are available.

B. Aquatic

No criteria for freshwater or marine life have been drafted (U.S. EPA, 1979).

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NITROSAMINES

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No. 138

N-Nitrosodiphenylamine

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

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N-NITROSODIPHENYLAMINE

SUMMARY

Formation of N-nitrosodiphenylamine (NDPhA) has been shown experimentally in the stomachs of individuals receiving nitrite and diphenylamine. N-nitrosodiphenylamine undergoes photochemical decomposition in solution or in the atmosphere in the presence of sunlight. Bacterial degradation of NDPhA has been demonstrated in soil.

Prior to the release of recent findings from the NCI bioassay program, NDPhA was considered a non-carcinogenic nitrosamine. In the NCI lifetime rat feeding study, however, NDPhA was found to induce a significant incidence of urinary bladder tumors in both males and females. Few urinary bladder tumors were observed in mice in a similar experiment, although there was a high incidence of non-neoplastic bladder lesions.

N-nitrosodiphenylamine has consistently been found negative in a variety of mutagenicity assays.

I. INTRODUCTION

This document is based on the Ambient Water Quality Criteria Document on Nitrosamines (U.S. EPA, 1979b), the Scientific and Technical Assessment Report on Nitrosamines (U.S. EPA, 1977), and other selected references. The term "N-nitrosodiphenylamine" (NDPhA) in this report refers specifically to that compound; the term "nitrosamine" when used in this report refers to nitrosamines in general.

N-nitrosodiphenylamine (NDPhA; molecular weight 198.23; molecular formula $C_{12}H_{10}N_2O$) is a yellow to brown or orange powder or flakes. It has the following physical/chemical properties (Hawley, 1977):

Melting Point:	64-66°C
Solubility:	insoluble in water; soluble in organic solvents.

NDPhA is used as a vulcanization retarder in the rubber industry (Hawley, 1977).

A review of the production range (includes importation) statistics for N-nitrosodiphenylamine (CAS No. 86-30-6) which is listed in the initial TSCA Inventory (1979a) has shown that between 400,000 and 900,000 pounds of this chemical were produced/imported in 1977.*/

II. EXPOSURE

A. Formation

The chemistry of formation of nitrosamines is quite complex, however, they are in general formed by the combination of amines (R_1R_2N-) with some nitrosating agent. Formation has been shown to occur with primary, secondary, and tertiary amines, as well as

*/ This production range information does not include any production/importation data claimed as confidential by the person(s) reporting for the TSCA Inventory, nor does it include any information which would compromise Confidential Business Information. The data submitted for the TSCA Inventory, including production range information, are subject to the limitations contained in the Inventory Reporting Regulations (40 CFR 710).

other amino compounds. The nitrosating agent can be derived from nitric oxides (NO, NO_2, N_2O_3, or N_2O_4) or inorganic nitrite (U.S. EPA, 1977).

The *in vivo* formation of nitrosamines following ingestion of precursors has been demonstrated in human and animal studies (U.S. EPA, 1977) Sander and Seif (1969) showed the formation of NDPhA in the stomachs of humans given nitrite and diphenylamine.

B. Environmental Fate

In the absence of light, nitrosamines are quite stable and will decompose hydrolytically only following prolonged contact with strong acid. There is no evidence of thermal instability of nitrosamines in the gas phase; however, they do undergo photochemical decomposition in solution or in the atmosphere in the presence of sunlight or ultra-violet light (U.S. EPA, 1977).

Transnitrosation reactions involving direct transfer of the nitroso group from NDPhA to other amines have been demonstrated (Challis and Osborn, 1972). Such a reaction yields a new N-nitroso compound and diphenylamine.

In unamended soil, 70% of added NDPhA was lost within 30 days. In soil amended with bacteria, added NDPhA had disappeared completely at the end of day 10 (Mallik, 1979).

C. Bioconcentration

See Section V.C.

III. PHARMACOKINETICS

Intestinal bacteria common in the gastrointestinal tract of many animals and humans have been shown capable of degrading NDPhA (Rowland and Grasso, 1975).

IV. HEALTH EFFECTS IN MAMMALS

A. Carcinogenicity

In a one-year study, Argus and Hoch-Ligeti (1961) administered NDPhA by gavage to 25 male rats for 45 weeks (total dose 244 mg/rat). No tumors were observed. In other studies (Boyland et al., 1968) no tumors were seen when 20 rats were given the test compound in the diet for 100 weeks at daily doses of 120 mg/kg, or when 24 male rats were administered DNPhA by intraperitoneal injection once per week for 6 months at a dose of 2.5 mg/week. Both tests were terminated after 2 years. When two groups of mice (18 male and 18 female per group) were administered NDPhA by gavage daily for 3 weeks at 1,000 mg/kg, then in diet at 3,769 ppm for 18 months, no significant incidences of tumors were observed. However, in another assay reticulum cell sarcomas were observed in the mice when the chemical was injected subcutaneously (NCI, 1968; Innes et al., 1969). Druckrey et al. (1967) reported a lack of tumorigenicity in rats administered 120 mg/kg/day of NDPhA for 700 days, for a total dose of 65 g/kg. Taken together, these studies were viewed as a demonstration of the non-carcinogenicity of NDPhA.

Recent results from the NCI bioassay program, however, have demonstrated that NDPhA is a carcinogen in rats (NCI, 1979; Cardy

et al., 1979). In these studies NDPhA was administered in the diet to rats and mice at two doses, the "maximum tolerated dose" for each species and one-half that amount. Groups of 50 animals of each sex were tested at each dose for approximately 100 weeks. The study found that dietary exposure to NDPhA gave rise to a significant incidence of urinary bladder tumors in both male (40%) and female (90%) rats. Few urinary bladder tumors were observed in the mice, although there was a high incidence of non-neoplastic bladder lesions. The authors (Cardy et al., 1979) ascribed the strong carcinogenic effect seen in rats in this study to the higher doses used; they estimated that the maximum daily intake of NDPhA was 320 mg/kg in females and 240 mg/kg in males. These levels are somewhat higher than those used by Druckrey et al. (1967) in the only other known chronic feeding study done in rats.

B. Mutagenicity

NDPhA has consistently been reported negative in a variety of mutagenicity assays: S. typhimurium (Ames test), with and without activation (Yahagi et al., 1977; Bartsch et al., 1976; Simmon, 1979a; Rosenkranz and Poirier, 1979); E. coli, with activation (Nakajima et al., 1974); (Pol A$^-$) E. coli (Rosenkranz and Poirier, 1979); N. crassa (Marquardt et al., 1963); Chinese hamster V79 (lung) cell line, with and without activation (Kuroki et al., 1977); Saccharomyces cerevisiae D3, with activation (Simmon, 1979b); host mediated assay (tester strains: S. typhimurium and S. cerevisiae D3) (Simmon et al., 1979); in vivo mouse testicular DNA synthesis assay (Friedman and Staub, 1976).

C. Other Toxicity

The oral LD_{50} in rats is 1650 mg/kg; in mice the oral LD_{50} is 3,850 mg/kg (NIOSH, 1978).

V. AQUATIC EFFECTS

A. Acute

The 96-hour LC_{50} for NDPhA in bluegill sunfish under static test conditions is 5.9 mg/l (nominal concentration). The 48-hour EC_{50} (static conditions) in Daphnia magna is 7.7 mg/l (nominal concentration). The adjusted 96-hour LC_{50} for the mummichog (a marine fish) under static conditions is 3,300 mg/l (nominal concentration) (U.S. EPA, 1979b).

B. Chronic

No adverse effects were reported at any test concentration in a chronic toxicity study in Daphnia magna at concentrations below 0.048 mg/l (U.S. EPA, 1979b).

C. Other

Bioconcentration of NDPhA by bluegill sunfish reached equilibrium within 14 days; the bioconcentration factor was 217. The half-life of the compound in bluegill sunfish was less than one day (U.S. EPA, 1979b).

VI. EXISTING GUIDELINES

Criteria for the protection of aquatic species from excess NDPhA exposure have not been established (U.S. EPA, 1979b).

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No. 139

N-Nitrosodi-n-propylamine

Health and Environmental Effects

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WASHINGTON, D.C. 20460

APRIL 30, 1980

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139-1

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated n-nitrosodi-n-propylamine and has found sufficient evidence to indicate that this compound is carcinogenic.

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N-NITROSODI-n-PROPYLAMINE

SUMMARY

The International Agency for Research on Cancer has concluded that "N-nitrosodi-n-propylamine should be regarded for practical purposes as if it were carcinogenic in humans." The conclusion is based on positive findings in several long-term animal studies with the compound. It has also been found mutagenic in several test systems with activation.

The chemistry of formation of nitrosamines is quite complex, however, they are formed in general by the combination of amines with some nitrosating agent. Nitrates, nitrites, and amines (primary, secondary, and tertiary), the precursors in the formation of nitrosamines, are ubiquitous in the environment. Significant quantities of the precursors are also produced through human activities.

The in vivo formation of nitrosamines following ingestion of precursors has been demonstrated in humans and animals.

Nitrosamines degrade in the presence of sunlight; however, in the dark they are quite stable. Microorganisms can function both in the formation and degradation of nitrosamines. The half-life of aliphatic nitrosamines in the environment ranges from one hour in the atmosphere in sunlight to more than 40 days in soils and water (in the absence of light).

I. INTRODUCTION

This document is based on the Ambient Water Quality Criteria Document for Nitrosamines (U.S. EPA, 1979a), Volume 17 of the

IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans (IARC, 1978), the Scientific and Technical Assessment Report on Nitrosamines (U.S. EPA, 1977), and other selected references. The term "N-nitrosodi-n-propylamine" (NDPA) in this report refers specifically to that compound; the term "nitrosamine" when used in this report refers in general to simple aliphatic nitrosamines.

N-nitrosodi-n-propylamine (NDPA; $C_6H_{14}N_2O$; molecular weight 130.2) is a yellow liquid having the following physical chemical properties (IARC, 1978).

Boiling Point:	81°C
Density:	d_4^{20} 0.9160
Solubility:	soluble in water, organic solvents, and lipids.
Volatility:	can be steam distilled quantitatively.

A review of the production range (includes importation) statistics for NDPA (CAS No. 621-64-7) which is listed in the initial TSCA Inventory (1979b) has shown that between zero and 900 pounds of this chemical were intentionally produced/imported in 1977.*/

*/ This production range information does not include any production/importation data claimed as confidential by the person(s) reporting for the TSCA Inventory, nor does it include any information which would compromise Confidential Business Information. The data submitted for the TSCA Inventory, including production range information, are subject to the limitations contained in the Inventory Reporting Regulations (40 CFR 710).

No information on the commercial uses of NDPA was located, however, it appears likely that most, if not all, of that produced is used solely in the laboratory.

II. EXPOSURE

Nitrates, nitrites, and amines (in this case the propylamines), which are precursors in the formation of nitrosamines, are ubiquitous in the environment and occur in food, water, soil, and air. The natural occurrence of nitrates, nitrites, and secondary and tertiary amines results from their formation during the nitrogen cycle. In addition to the naturally formed precursors, significant quantities are produced through human activities (U.S. EPA, 1977). Some of the major man-made sources of the precursors are listed in Table 1.

A. Formation

The chemistry of formation of nitrosamines is quite complex, however, they are formed in general by the combination of amines (R_1R_2N-) with some nitrosating agent. Formation has been shown to occur with primary, secondary, and tertiary amines, as well as other amino compounds. The nitrosating agent can be derived from nitric oxides (NO, NO_2, N_2O_3, or N_2O_4) or inorganic nitrite. Certain factors (catalysts) can affect the rate of nitrosation. Depending on the reactants and catalysts that are present, nitrosation can occur under acidic, neutral, or alkaline conditions. Nitrosation of amines can also occur by transnitrosation involving other, more labile N-nitroso compounds (U.S. EPA, 1977; Mirvish, 1977).

Table 1. Man-Made Sources of Nitrosamine Precursors (U.S. EPA, 1977)

Nitric Oxides	Amines
Transportation	Feedlots
Motor vehicles	Rendering plants
Aircraft	Antioxidants
Railroads	Vulcanization accelerators
Fuel combustion in stationary sources	Pharmaceuticals
Coal	Self-polishing waxes
Fuel Oil	Synthetic detergents
Natural gas	Pesticides
Wood	Solvents
Industrial processes	Corrosion inhibitors
Solid waste disposal	Animal glues
Miscellaneous	Photographic products
Forest fires	Leather tanning
Structural fires	Primary amine production
Coal refuse	
Agricultural	

The *in vivo* formation of nitrosamines following the ingestion of precursors has been demonstrated in human and animal studies (U.S. EPA, 1976,).

Nitrosamines can be formed in soil, water, and sewage under appropriate conditions (Ayanaba *et al.*, 1973a, b; Ayanaba and Alexander, 1974; Kohl *et al.*, 1971). Microorganisms in soil and water can participate in the formation of nitrosamines (Ayanaba *et al.*, 1973b; Mills and Alexander, 1976), although microbial involvement in such formation reactions is not essential (Mills, 1976; Mills and Alexander, 1976).

B. Environmental Fate

In the absence of light, nitrosamines are quite stable and will decompose hydrolytically only following prolonged contact with strong acid. There is no evidence of thermal instability of nitrosamines in the gas phase; however, they do undergo photo-

chemical decomposition in solution or in the atmosphere in the presence of sunlight or ultra-violet light. There are very few quantitative studies on the rate of photochemical degradation of nitrosamines or on the rate effects of other factors (U.S. EPA, 1977; IARC, 1978). Nonetheless, it has been shown that N-nitrosodimethylamine has an atmospheric half-life (during ambient atmospheric conditions) of between 30 minutes and one hour in sunlight (Hanst et al., 1977). The atmospheric half-life of NDPA should be similar (U.S. EPA, 1979a).

N-nitrosodi-n-propylamine appears to be fairly resistant to microbial attack under environmental conditions. The soil half-life of NDPA under varying conditions has been reported as ranging between 10 and 40 days (Tate and Alexander, 1975; Saunders et al., 1979; Oliver et al., 1978). In lake water under laboratory conditions, NDPA persisted for more than 4 months (Tate and Alexander, 1975).

A laboratory soil leaching study (Saunders et al., 1979) has indicated that NDPA (which is about 1% soluble in water) will leach under heavy simulated rainfall conditions. In a field study, however, NDPA did not leach below a depth of 20 cm. The authors suggest that under field conditions, NDPA is dissipated due to volatilization and degradation.

C. Bioconcentration

No information on the bioaccumulation potential of NDPA was located, although it should be fairly low.

D. Environmental Occurrence

NDPA has been detected in food, alcoholic beverages, and several pesticides (IARC, 1978). It has also been detected in

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the waste-water from several chemical plants (Cohen and Bachman, 1978).

III. PHARMACOKINETICS

A. Absorption

In goats, one hour after oral administration, NDPA was found in milk and blood, indicating fairly rapid uptake. Only traces were found in the milk after 24 hours (Juszkiewicz and Kowalski, 1974).

B. Distribution

No information was located on the distribution of NDPA; however, simple aliphatic nitrosamines tend to distribute rapidly and fairly uniformly in the body (U.S. EPA, 1979a).

C. Metabolism

Available evidence suggests that NDPA must be metabolically activated to exert its toxic and carcinogenic effects. Urine collected during the 48 hours after oral administration of an LD_{50} dose of NDPA to rats contained the following compounds: N-nitroso-3-hydroxy-n-propyl-n-propylamine, N-nitroso-2-carboxy-ethyl-n-propylamine, and to a lesser extent, N-nitrosocarboxy-methyl-n-propylamine, and N-nitroso-2-hydroxy-n-propyl-n-propylamine (Blattman and Preussmann, 1973). The last named metabolite, N-nitroso-2-hydroxy-n-propyl-n-propylamine, has been found carcinogenic in rats (Reznik et al., 1975) and hamsters (Pour et al., 1974a,b), thus it may be the active carcinogenic metabolite (proximate and/or ultimate carcinogen) of NDPA.

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IV. HUMAN HEALTH EFFECTS

A. Carcinogenicity

Groups of rats were given NDPA in the drinking water at doses of 4, 8, 15, or 30 mg/kg day. Of the 48 animals on test, 45 developed liver carcinomas, 8 developed papillomas or carcinomas of the esophagus, and 6 showed carcinomas of the tongue (Druckrey et al., 1967).

Groups of rats were injected subcutaneously with 1/5, 1/10, or 1/20 the LD_{50} of NDPA (LD_{50}: 487 mg/kg) once weekly for life. The average total dose of NDPA ranged between 0.93 and 2.7 g/kg. A high incidence of neoplasms was observed in the nasal cavities. In addition, tumors of the liver, lung, kidney, and esophagus were observed (Althoff et al., 1973a; Reznik et al., 1975).

Groups of Syrian golden hamsters were injected subcutaneously with 1.2% NDPA in olive oil once weekly for life at 5 dose levels (highest dose was 60 mg/kg). Tumors were observed in the nasal cavities, laryngobronchial tract, lungs, and a variety of other organs (Althoff et al., 1973b; Pour et al., 1973).

The International Agency for Research on Cancer (1978) has concluded:

> There is sufficient evidence of a carcinogenic effect of N-nitrosodi-n-propylamine in two experimental animal species. Although no epidemiological data were available...N-nitrosodi-n-propylamine should be regarded for practical purposes as if it were carcinogenic to humans,

B. Mutagenicity

NDPA was positive in the Ames test (S. typhimurium strains TA 1530, TA 1535, and TA 100) with activation (Barstch et al.,

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1976; Camus et al., 1976; Olajos and Cornish, 1976; Sugimura et al., 1976). NDPA was also mutagenic in E. coli (Nakajima et al., 1974) and in Chinese hamster V79 cells (Kuroki et al., 1977), in both cases with activation.

C. Other Toxic Effects

The acute oral LD_{50} of NDPA was 480 mg/kg in rats (Druckrey et al., 1967); the subcutaneous LD_{50} was 487 mg/kg in rats and 600 mg/kg in hamsters (Pour et al., 1973; Reznik et al., 1975).

V. AQUATIC EFFECTS

No data on the aquatic effects of NDPA were located.

VI. EXISTING GUIDELINES

The class of compounds "nitrosamines" was included in the American Conference of Governmental Industrial Hygienists (1977) list of "Industrial Substances Suspected of Carcinogenic Potential for Man." No threshold limit value (TLV) was given.

As noted in Section IV.A, the International Agency for Research on Cancer (1978) has concluded that "N-nitrosodi-n-propylamine should be regarded for practical purposes as if it were carcinogenic to humans."

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No. 140

Paraldehyde

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

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PARALDEHYDE

Summary

There is no evidence in the available literature to indicate that paraldehyde, a central nervous system depressant, is carcinogenic, mutagenic, or teratogenic.

In low doses (4-8 ml) paraldehyde has a hypnotic effect on the central nervous system. Following chronic and acute exposures at higher concentrations, paraldehyde affects the respiratory and circulatory systems.

Data concerning the effects of paraldehyde on aquatic organisms were not found in the available literature.

Guidelines or standards concerning air or water exposures were not found in the available literature.

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PARALDEHYDE

I. INTRODUCTION

Paraldehyde, 2,4,6-trimethyl-1,3,5-trioxane, also known as para-acetaldehyde, is a colorless liquid with a molecular weight of 132.2. This compound melts at 13°C and boils at 125°C. It has a specific gravity of 0.994 at 20°C, and its solubility in water is 120,000 mg/l at 13°C and 58,000 mg/l at 100°C (Verschueren, 1977). The odor of paraldehyde is not pungent or unpleasant, but it is characterized by a disagreeable taste (Wilson, et al. 1977).

Paraldehyde was introduced into medicine by Ceruello in 1882 as the second synthetic organic compound to be used as a sedative hypnotic (Wilson, et al. 1977). It is used frequently in delirium tremens and in treatment of psychiatric states characterized by excitement when drugs must be given over a long period of time (Wilson, et al. 1977). It also is administered for intractable pain which does not respond to opiates and for basal and obstetrical anaesthesia (Goodman and Gilman, 1970). It is effective against experimentally induced convulsions and has been used in emergency therapy of tetanus, eclampsia, status epilepticus, and poisoning by convulsant drugs (Goodman and Gilman, 1970).

It is used primarily in medicine, and therefore, the chance of accidental human exposure or environmental contamination is low. However, paraldehyde decomposes to acetaldehyde and acetic acid (Gosselin, et al. 1976); these compounds have been found to be toxic. In this sense, occupational exposure or environmental contamination is possible. Since paraldehyde is prepared from acetaldehyde by polymerization in the presence of an acid catalyst, there exists a potential for adverse effects, although none have been reported in the available literature.

II. EXPOSURE

No monitoring data are available to indicate ambient air or water levels of the compound. Human exposure to paraldehyde from ingestion cannot be assessed, due to a lack of monitoring data. No data on dermal exposure of humans were found in the available literature.

III. PHARMACOKINETICS

Paraldehyde is rapidly absorbed from the gastrointestinal tract and parenteral sites. Following oral administration to rats, the maximum concentration in the brain is reached within 30 minutes (Figot, et al. 1953). A significant percentage is excreted unchanged through the lungs. Lang, et al. (1969) reported that human subjects given unspecified oral doses exhaled 7 percent of the administered dose within 4 hours. Only traces are observed in the urine; the rest is metabolized by the liver. There is indirect evidence that paraldehyde is depolymerized to acetaldehyde in the liver, then oxidized by aldehyde dehydrogenase to acetic acid which, in turn, is ultimately metabolized to carbon dioxide and water in mice (Hitchcock and Nelson, 1943).

No data on bioaccumulation of paraldehyde were found in the available literature. Based on the evidence of metabolism above, however, significant bioaccumulation would appear unlikely.

IV. EFFECTS

A. Carcinogenicity

Paraldehyde has been designated a "suspect carcinogen" (NIOSH, 1978), although no increase in neoplasms was observed in the mouse-skin painting study (Row and Salaman, 1955), which was cited by NIOSH.

B. Mutagenicity, Teratogenicity and Other Reproductive Effects.

Pertinent data could not be located in the available literature.

C. Chronic Toxicity

In low doses (4-8 ml), paraldehyde has found use as a therapeutic agent. However, if used for a prolonged period of time, intoxication results in tolerance and dependence. Paraldehyde addiction resembles alcoholism; withdrawal may result in delirium tremens and vivid hallucinations (Goodman and Gilman, 1970).

Acidosis, bleeding gastritis, muscular irritability, azotemia, oliguria, albuminuria, leukocytosis, fatty changes in the liver and kidney with toxic hepatitis and nephrosis, pulmonary hemorrhages, edema, and dilation of the right heart have all been observed in cases of chronic paraldehyde poisoning. Metabolic acidosis is a manifestation of paraldehyde intoxication in the paraldehyde addict. The etiology of the acidosis is uncertain (Beier, et al. 1963).

D. Acute Toxicity

Figot, et al. (1953) reported an oral LD_{50} of 1.65 g/kg for paraldehyde in rats. These investigators reported that the level of paraldehyde in the brain was predictive of the degree of toxicity. The median brain concentration lethal to rats was 47 mg percent.

In humans, therapeutic oral doses of 4-8 ml induce sleep. At this dose, little effect on respiration or blood pressure is seen. There appears to be little margin of safety, and slight increases in dosage may result in poisoning. The poisoned patient commonly exhibits very rapid, labored respiratory movements (Goodman and Gilman, 1970). Accompanying the rapid respiration is a marked depression of blood pressure which persists for several hours. Degenerative changes in the kidney and liver have also been observed (Kirk and Othmer, 1979). Unfortunately, it is not absolutely certain whether these effects are due to paraldehyde or to its decomposition products, acetaldehyde and acetic acid.

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Toxic doses of unspecified amounts, given intravenously, cause diffuse, massive pulmonary hemorrhages and edema, as well as dilation of the right heart. Adverse effects, as seen in cases of severe acute paraldehyde intoxication, resemble those seen in chronically exposed individuals, e.g., addicts.

Metabolic acidosis is also found in the severe acute cases. Hayward and Boshell (1957) produced metabolic acidosis and other toxic effects, including pulmonary edema in dogs, by administering unspecified amounts of deteriorated paraldehyde through gastric tubes over a period of 18 hours. In this case it is uncertain whether the paraldehyde or the deteriorated product was the cause of the observed effects. The same is true in another study where a deteriorated product (40 percent acetic acid) produced sudden death with intense corrosion of buccal mucosa and upper air passages. Rectal administration (a common route in therapeutic settings) in another poisoning victim caused great pain and sloughing of rectal mucosa (Gosselin, et al. 1976).

High concentrations (unspecified) depressed cholinergic junctions in frogs, apparently by reducing the amount of acetylcholine liberated from nerve endings (Nicholls and Quillam, 1956; Quillam, 1959).

The lethal dose in humans is disputable. Less than one ounce by mouth has been shown to be lethal in some cases, while others have tolerated four ounces. Death results from respiratory failure preceded by prolonged and profound coma (Goodman and Gilman, 1970).

Paraldehyde has been used in obstetrics; however, it readily crosses the placental barrier and appears in the fetal circulation. Undesirable effects, including delay in respiratory movements, have been

observed in neonates following administration to the mother during labor (Goodman and Gilman, 1970). Consequently, paraldehyde finds little or no use in obstetrics today.

The lowest dose of paraldehyde reported to produce any toxic effect (unspecified) in humans is 121 mg/kg. Oral LD_{50} values have been reported for the following species: rats, 1530 mg/kg; rabbits, 3304 mg/kg; and dogs, 3500 mg/kg. NIOSH (1978) has reported the lowest lethal innalation concentration to be 2000 ppm.

V. AQUATIC TOXICITY

Data concerning the effects of paraldehyde on aquatic organisms were not found in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

No exposure limits or standards were found in the available literature to exist for air or water.

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No. 141

Pentachlorobenzene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

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PENTACHLOROBENZENE

Summary

Oral feeding of pentachlorobenzene to pregnant rats has produced developmental effects and decreased body weights in fetuses. No adverse reproductive or developmental effects were seen in mice following maternal administration of the compound orally.

There is no information available on the mutagenic effects of pentachlorobenzene.

A single study has alluded to carcinogenic effects of pentachlorobenzene in mice and lack of carcinogenic effects in dogs and rats. The details of this study were not available for evaluation.

Reported 96-hour LC_{50} values for the bluegill, mysid shrimp, and sheepshead minnow range from 250 to 830 µg/l. Daphnia is considerably less sensitive. Studies with algae, with 96-hour EC_{50} values based on chlorophyll a concentration, have reported values ranging from 2,000 to 7,000 µg/l. The steady-state bioconcentration factor for the bluegill is 1,800.

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I. INTRODUCTION

Pentachlorobenzene, CAS registry number 608-93-5, is a colorless crystalline solid with a pleasant aroma. It is produced mainly as a byproduct of other chlorobenzenes and has the following physical and chemical properties (Windholz, 1976; Weast, 1972; Hawley, 1971):

Formula:	C_6HCl_5
Molecular Weight:	250.34
Melting Point:	86°C
Boiling Point:	277°C
Density:	$1.8342^{16.5}$
Solubility:	Soluble in carbon disulfide, chloroform, and hot alcohol, insoluble in water

Pentachlorobenzene is used primarily as a precursor in the synthesis of the fungicide pentachloronitrobenzene, and as a flame retardant.

II. EXPOSURE

A. Water

Burlingame (1977) has identified pentachlorobenzene in the effluent from a wastewater treatment plant in southern California. Access to water can occur by industrial discharge or from the degradation of other organochlorine compounds.

B. Food

Pentachlorobenzene has been detected in plants (Balba and Saha, 1974; Kohli, et al. 1976a) and in animal fat (Stijve, 1971; Saha and Burrage, 1976; Greve, 1973), and was shown to arise from the metabolic breakdown of lindane or other organochlorine compounds. The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for pentachlorobenzene to be 7,800 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on steady-state bioconcentration studies in bluegills.

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C. Inhalation

The primary site for inhalation exposure could be the workplace in industries utilizing or producing pentachlorobenzene.

D. Dermal

Pertinent data could not be located in the available literature.

III. PHARMACOKINETICS

A. Absorption

From studies with rabbits it would appear that pentachlorobenzene is very poorly absorbed from the gastrointestinal tract (Parke and Williams, 1960).

B. Distribution

The distribution of pentachlorobenzene favors retention in the fat (Parke and Williams, 1960). Khera and Villeneuve (1975) have found widespread tissue distribution of the compound following oral administration to pregnant rats and accumulation in fetal tissues.

C. Metabolism

There appear to be some qualitative and quantitative differences between species in the metabolism of pentachlorobenzene. In the rat and rabbit, pentachlorobenzene was shown to be metabolized to a variety of isomers of tetrachlorophenol, with the amount of unchanged pentachlorobenzene excreted in the urine of the rabbit being one percent (Kohli, et al. 1976b), and in the rat being nine percent (Koss and Koransky, 1977). Kohli and coworkers (1976b) suggest that the dechlorination hydroxylation step to the tetrachlorophenol derivative proceeds through an arene oxide intermediate.

D. Excretion

In rats and rabbits urinary excretion of metabolites or unchanged pentachlorobenzene predominated. Rozman, et al. (1978) found the biological half-life of pentachlorobenzene to be two to three months in rhesus monkeys.

After 40 days, ten percent of the total dose was secreted in the urine; of this, 58 percent was pentachlorophenol. After the same period, about 40 percent of the dose was excreted in the feces, 99 percent as pentachlorobenzene. The authors suggest that biliary excretion was occurring.

IV. EFFECTS

A. Carcinogenicity

There is one report, which could not be critically evaluated, which alludes to pentachlorobenzene being carcinogenic in mice but not in rats or dogs (Preussman, 1975).

B. Mutagenicity

Pertinent data could not be located in the available literature.

C. Teratogenicity

Rats receiving 50, 100, and 200 mg/kg pentachlorobenzene on days 6 to 15 of gestation had pups with increased suprauni ribs at all doses (Khera and Villeneuve, 1975). The high dose also produced sternal defects consisting of unossified or nonaligned sternabrae with cartilagenous precursors present. The authors did not consider these defects to be teratogenic.

D. Other Reproductive Effects

Oral administration of pentachlorobenzene (50 or 100 mg/kg) to pregnant mice on days 6 to 15 of gestation produced no teratogenic or adverse reproductive effects (Courtney, et al. 1977).

E. Chronic Toxicity

Pertinent data could not be located in the available literature.

V. AQUATIC TOXICITY

A. Acute

The U.S. EPA (1978) reported 96-hour LC_{50} values for the bluegill (Lepomis macrochirus) exposed to pentachlorobenzene to be 250 µg/l.

The 48-hour EC_{50} value reported for Daphnia magna is 5,280 µg/l (U.S. EPA, 1978). For the saltwater species, sheepshead minnow (Cyprinodon variegatus) and mysid shrimp (Mysidopsis bahia), the determined 96-hour LC_{50} values are 830 and 160 µg/l, respectively.

B. Chronic

Pertinent data could not be located in the available literature.

C. Plant Effects

The reported 96-hour EC_{50} value for Selenastrum capricornatum based on chlorophyll a concentration is 6,780 µg/l (U.S. EPA, 1978). For the marine alga Skeletonema costatum, a 96-hour EC_{50} value on the same basis is 1,980 ug/l (U.S. EPA, 1978).

D. Residue

After a 28-day exposure, the steady-state bioconcentration factor for the bluegill for pentachlorobenzene is 1,800. The half-life is greater than seven days (U.S. EPA, 1978).

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The U.S. EPA (1979) has drafted a criterion of 0.5 µg/l for the protection of human health.

B. Aquatic

No criteria have been developed or proposed to protect aquatic organisms from pentachlorobenzene toxicity due to the lack of pertinent data.

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No. 142

Pentachloronitrobenzene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated pentachloronitrobenzene and has found sufficient evidence to indicate that this compound is carcinogenic.

DISCLAIMER

The mention of company trade names or products does not constitute endorsement by the U.S. EPA or the Federal government.

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PENTACHLORONITROBENZENE

Summary

Increased incidence of hepatoma formation was reported in hybrid mice treated with pentachlorobenzene (PCNB). PCNB was found to be mutagenic in the hcr-strain of Escherichia coli ochre, but not in another E. coli strain.

PCNB containing a number of contaminants produced renal agenesis and cleft palate in C57Bl/6 mice, cleft palate in CD-1 mice, but was not teratogenic in CD rats. Purified PCNB (less than 20 ppm hexachlorobenzene) resulted in fewer cleft palates in the fetuses. No significant teratogenic effects in rats were detected at dosages as high as 1,563 ppm. In a three generation study using doses as high as 500 ppm, PCNB had no significant effects on the reproduction of rats.

Acute toxicity data for fish were: a 96-hour LC_{50} in bluegill from 0.29 to 0.38 ppm and a 96-hour LC_{50} of 0.31 ppm in rainbow trout.

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I. INTRODUCTION

This profile is based on the Initial Scientific Review of Pentachloronitrobenzene, PCNB, plus relevant scientific research articles published subsequent to that document (U.S. EPA, 1976).

Pentachloronitrobenzene (molecular weight, 295.34) is a pale yellow-to-white solid, depending on purity, that melts between 142° and 146°C, has a boiling point of 328°C at 760 mm Hg, and a density of 1.718 g/cm^3 at 25°C. Reported vapor pressure values for PCNB are: 1.16×10^{-5} mm Hg at 10°C, 5.0×10^{-5} mm Hg at 20°C, and 11.3×10^{-5} mm Hg at 25°C (U.S. EPA, 1976). PCNB has a relative vapor density (air = 1) of 10.2 (Verschueren, 1977). Water solubility of PCNB is 0.44 mg/l at 20°C and 2 mg PCNB will dissolve in one liter ethanol at 25°C. PCNB is freely soluble in carbon disulfide, benzene, chloroform, ketones, and aromatic and chlorinated hydrocarbons, and slightly soluble in alkanols (U.S. EPA, 1976).

PNCB is primarily registered as a soil fungicide for a wide variety of crops and is also used as a seed-treatment fungicide. It is effective against bunt of wheat, Botrytis, Rhizoctonia, and Sclerotinia spp. There are no current nonagricultural uses of PCNB (U.S. EPA, 1976). PCNB is manufactured domestically under the trade name Terraclor® with an estimated annual production in 1971 of 3 million pounds (U.S. EPA, 1972). According to the Olin Corporation (1974), 60 to 70 percent of the PCNB produced will be used in the United States. The United States has imported from 20,000 to 132,000 lbs. between 1966 and 1969 (U.S. EPA, 1976). PCNB manufactured in Europe is marketed under the common name Quintozene (Dejonckheere, et al.

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1976). It may be worth noting that commercial PCNB fungicides contain impurities such as hexachlorobenzene, pentachlorobenzene and tetrachloronitrobenzene, which may be more hazardous than PCNB itself (Dunn, et al. 1978; Simon, et al. 1979).

No data are available for the disassociation of PCNB in aqueous systems. Crosby and Hamadmad (1971) studied the photoreduction of PCNB. The compound remained unchanged in sunlight, probably excluding photolysis as a major route of environmental degradation. At temperatures above 328°C, some decomposition of PCNB has been noted (U.S. EPA, 1976).

PCNB can be biodegraded by pure cultures of actinomycetes and filamentous fungi during their active growth phase (Chacko, et al. 1966).

II. EXPOSURE

PCNB is prepared by either chlorination or nitration reactions. The reaction temperature for the chlorination process is 60 to 70°C. Although this reaction is well below the boiling point of PCNB, atmospheric emissions are possible because of PCNB's relatively high vapor pressure. Furthermore, there exists a potential for environmental release via wastewater effluents at the manufacturing sites. No monitoring data are available for ambient air or water levels of the compound. The major source of environmental contamination is through its application as a fungicide. In the United States, PCNB is used primarily on cotton and peanut crops. Geographic use distribution is mainly concentrated west of the Mississippi River (U.S. EPA, 1976). Carey, et al. (1979) in their study of pesticide residues in the soil detected PCNB in only three of the 1,483 sample sites. The detected residue concentration was from 0.22 to 2.61 ppm. It should be noted, however, that their study was primarily confined to the eastern United States.

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Routes of human exposure to PCNB include water, air, contaminated foods, and fish. Casanova and Dubroca (1973) studied the residues of PCNB found in lettuce grown in soil treated with the fungicide. Residue values were 0.73 ppm (15 kg PCNB/ha) and 1.56 ppm (45 kg PCNB/ha). Goursaud, et al. (1972) detected PCNB contamination in endive roots. Since the main objective of their study was the uptake of hexachlorobenzene, actual PCNB concentrations were not noted. However, in a subsequent experiment Goursaud, et al. (1972) fed cows endive roots containing 2.16 ppm PCNB. PCNB residues found in the cows' milk were negligible. Bioaccumulation of PCNB in White Leghorn cockerels (Dunn, et al. 1978) was also found to be negligible (accumulation ratio 0.001 = tissue concentration/dietary concentration). Broiler chickens (Reed, et al. 1977) did not accumulate PCNB or its metabolites to any appreciable extent (0.002 ppm). No additional information on the levels of PCNB in foods is available.

Bioaccumulation data on PCNB were not found in the literature for aquatic organisms. Ko and Lockwood (1968) reported that the mycelium of fungi had accumulated a concentration of PCNB seven times that of the surrounding soil.

III. PHARMACOKINETICS

A. Absorption

Absorption data on PCNB were restricted to oral administration involving three test species. Betts, et al. (1955) reported that 60 percent of the oral dosage was not absorbed from the gastrointestinal tract in rabbits. Two subsequent studies, however, report that PCNB is readily absorbed from the gastrointestinal tract and/or metabolized by gut flora to another compound and then almost fully absorbed. Kögel, et al. (1979) found that PCNB was readily and almost completely absorbed from the gastrointestinal

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tract of Rhesus monkeys. After a single dose of 2 mg/kg given in methyl cellulose suspension, only 7.4 percent of the administered amount was excreted as unmetabolized PCNB in the feces. When 91 mg/kg PCNB was given in sesame oil, only 4.3 percent of the dose was excreted unmetabolized. Uptake occurs mainly by the portal venous route, with little involvement of the lymphatic system, bringing the absorbed PCNB directly to the liver where biotransformation can begin. Studies of Comet Red and White Leghorn chickens yielded similar results. Chickens fed 300 ppm PCNB in laying mash for sixteen weeks excreted only 1.1 ppm PCNB (Simon, et al. 1979).

B. Distribution

Several studies have been conducted on the distribution and storage of ingested PCNB. Due to rapid metabolism and elimination, this compound shows very little accumulation in body tissues. Betts, et al. (1955) used rabbits and Borzelleca, et al. (1971) employed beagles and rats. In neither experiment was PCNB detected in liver, kidney, muscle, or adipose tissue. Other studies have indicated very low concentrations of PCNB in various tissues. Simon, et al. (1979) found PCNB at concentrations of 0.85 ppm in fat and 0.005 ppm in egg whites of chickens fed 300 ppm PCNB for sixteen weeks. Other tissues examined contained no detectable levels of PCNB. Dunn, et al. (1978) found the highest tissue residues of PCNB in adipose tissue (1.14 and 1.87 ppm) and the gizzard (1.60 and 0.84 ppm) in chickens given 100 ppm and 1,000 ppm PCNB in feed, respectively. Leg and breast muscles and heart, kidney, and liver contained very low (0.16 to 0.07 ppm) or trace amounts of PCNB.

Concentrations of PCNB in various organs of Rhesus monkeys after chronic feeding of 2 ppm PCNB in the daily diet were (in ppm): blood, 0.07; muscle, 0.01; brain, 0.03; liver, 0.19; kidney, 0.14; adrenal cortex, 0.08;

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thymus, 0.20; lymph nodes (large intestine), 0.12; bone marrow, 0.13; and omental fat, 0.21 (Mueller, et al. 1978). Kögel, et al. (1979) found the highest concentration of PCNB and/or its metabolites occurring in bile (7.73 ± 0.2 ppm in males and 3.72 ± 0.05 in females) after feeding of 2 ppm PCNB for 70 days.

C. Metabolism

PCNB metabolism has been studied in rats, dogs, cows, and rabbits. Pentachloroaniline and methyl pentachlorophenyl sulfide are the major metabolites. Tissue retention of these compounds is found primarily in body fat with minimal concentrations found in muscle (U.S. EPA, 1976). Two major pathways for the biotransformation of PCNB in Rhesus monkeys are: 1) the reduction of the nitro-moeity to the corresponding aniline, and 2) the cleavage of the C-N bond, presumably via conjugation with sulfur-containing amino acids (Kögel, et al. 1979).

D. Excretion

PCNB and its metabolites are excreted mainly in the urine and feces. Mueller, et al. (1978) reported that Rhesus monkeys excreted almost 80 percent of the ingested PCNB within 5 days; of the excreted radioactivity, 91.2 percent was in the form of metabolites.

IV. EFFECTS

A. Carcinogenicity

Very little information on possible carcinogenic effects of PCNB was found in the available literature. Courtney, et al. (1976) cite one study which found PCNB to be carcinogenic in a hybrid mouse with an increased incidence of hepatoma formation. Levels of exposure were not given.

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B. Mutagenicity

PCNB was found to be mutagenic in the hcr-strain of Escherichia coli B/r ochre, but not in another E. coli strain. In the host-mediated assay in mice, no significant increase in mutation rates in Salmonella typhimurium and Serratia morcescens was observed after subcutaneous injection of PCNB. The compound also gave negative results in spot tests (U.S. EPA, 1976).

C. Teratogenicity and Other Reproductive Effects

PCNB was administered to pregnant rats by intubation on days 6 and 15 of gestation at dosages from 100 to 1,563 ppm. Fetuses were examined for gross malformations. No significant effects on the number of corpora lutae, the position and numbers of dead or resorbed fetuses, or the fetal weights and sex ratios were observed at any dose level. No significant skeletal or soft tissue anomalies were reported in the fetuses (U.S. EPA, 1976).

A three-generation study with groups of rats fed diets containing 0, 5, 50 or 500 ppm (Olin technical PCNB) showed no significant effects on fertility, gestation, viability, lactation, rats born per litter, or rats weaned per litter or their average weaning weights (U.S. EPA, 1976).

PCNB containing a number of contaminants, however, produced renal agenesis and cleft palate in C56Bl/6 mice and cleft palate in CD-1 mice, but was not teratogenic in CD rats. Purified PCNB (less than 20 ppm hexachlorobenzene) resulted in few cleft palates in fetuses (Courtney, et al. 1976).

D. Chronic Toxicity

PCNB does not appear to be chronically toxic when administered in feeding studies. Rhesus monkeys given 2 ppm or 91 ppm PCNB in their diet for 70 days were monitored for clinical chemistry and hematology parameters throughout the study. These parameters remained unchanged, indicating that

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organ function and hematopoiesis was not affected by PCNB or its metabolites (Kögel, et al. 1979).

White Leghorn chickens fed PCNB at concentrations up to 1,000 ppm for the first 8 weeks of life did not develop tissue lesions and hens fed up to 1,000 ppm for 35 weeks failed to develop histopathological changes (Dunn, et al. 1978).

Kögel, et al. (1979) cite studies which report that the toxic effect of Terraclor^{R} in rats and dogs is limited to liver enlargement due to hepatocellular hypertrophy. Also, cats had increased methemoglobin levels after moderate and high doses of Terraclor^{R} and dogs fed a very high dose (5,000 ppm) of PCNB of undetermined purity for two years were found to have reduced hematopoiesis. These effects, however, may be due to the presence of hexachlorobenzene as a contaminant (Kögel, et al. 1979).

E. Acute Toxicity

Cholakis, under contract with the U.S. EPA, administered single doses of pentachloronitrobenzene by gavage to several species of microtine rodents (voles) (U.S. EPA, 1978). The acute oral LD_{50} values in male and female M. montanus were 4,194 mg/kg and 3,717 mg/kg, respectively. In M. ochrogaster, M. canicaudus, and M. pennsylvanicus, values were greater than 5,000 mg/kg for both sexes. Toxicologic signs observed were some piloerection, loss of righting reflex and lachrymation. Most signs disappeared after 24 hours. Most deaths occurred within two to six days of dosing.

V. AQUATIC TOXICITY

A. Acute Toxicity

In static, acute toxicity bioassays using various PCNB formulations, bluegill (Lepomis macrochirus) had 96-hour median lethal concentration (LC_{50}) values ranging from 0.29 to 0.38 ppm. Rainbow trout (Salmo

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gairdneri) had a 96-hour LC_{50} value of 0.31 ppm (U.S. EPA, 1976).

B. Chronic Toxicity, Plant Effects and Residues

Pertinent data could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

No guidelines or standards were located in the available literature for humans or aquatic life.

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No. 143

Pentachlorophenol

Health and Environmental Effects

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PENTACHLOROPHENOL

SUMMARY

Pentachlorophenol has shown no evidence of carcinogenicity. Evidence for mutagenicity is equivocal. Pentachlorophenol is teratogenic in experimental animals at levels which produce maternal or fetal toxicity. Adverse health effects have been minimal in workers chronically exposed to pentachlorophenol. Relatively high levels of continous exposure produce muscle weakness, headache, anorexia, abdominal pain, weight loss, and irritation of skin, eyes, and respiratory tract. Pentachlorophenol is a strong uncoupler of oxidative phosphorylation.

Pentachlorophenol has been demonstrated to be acutely toxic to freshwater salmonids at levels as low as 37 µg/l. Comparable levels of toxicity were observed for marine fish. Freshwater plants were also highly susceptible to the action of this chemical with effective concentrations as low as 7.5 µg/l.

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PENTACHLOROPHENOL

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Pentachlorophenol (U.S. EPA, 1979).

Pentachlorophenol (PCP; C_6Cl_5OH; molecular weight 266.35) has the following physical and chemical properties (Stecher, 1968; Natl. Fire Prot. Assoc., 1973; Sax, 1975; Spector, 1956; Weast, 1975-76):

Melting Point Range	190 - 191° C
Boiling Point Range	309 - 310° C (decomposes)
Vapor Pressure	0.12 mm Hg at 100° C
Solubility	Water: 14 mg/l at 20° C

Commercial preparations of pentachlorophenol contain "caustic insolubles" or "nonphenolic neutral impurities" such as octachlorodibenzofurans and tetra-, penta-, hexa-, hepta-, and octachlorodibenzo-p-dioxins (Johnson, et al. 1973; Schwetz, et al. 1974). In addition, commercial pentachlorophenol contains three to ten percent tetrachlorophenol (Goldstein, et al. 1977; Schwetz, et al. 1978).

Pentachlorophenol is a commercially produced bactericide, fungicide, and slimicide used primarily for the preservation of wood, wood products, and other materials. As a chlorinated hydrocarbon, PCP is also used as a herbicide, insecticide, and molluscicide (U.S. EPA, 1979).

Pentachlorophenol and its sodium salt are widely disseminated in the environment (U.S. EPA, 1979). Pentachlorophenol undergoes photochemical degradation in solution in the presence of sunlight (Mitchell, 1961; Hanadmad, 1967; Wong and Crosby, 1977) and is reported to persist in warm moist soils for a period

of 12 months (Harvey and Crafts, 1952). In laboratory experiments, some microorganisms have been reported to metabolize pentachlorophenol and its sodium salt (Watanabe, 1973; Suzuki and Nose, 1971; Cserjesi, 1967; Reiner, et al. 1977).

II. EXPOSURE

Residues of pentachlorophenol have been found in food, water and human tissues. Pentachlorophenol levels of 0.06 µg/l in finished drinking water prepared from untreated water containing 0.17 µg/l have been reported (Buhler, et al. 1973). Pentachlorophenol has been detected in 13 of 240 food composites at levels of 0.01 to 0.04 mg/kg (Johnson and Manske, 1977). The calculated daily dietary exposure is one to six µg/person/day (Duggan and Corneliusen, 1972).

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor of pentachloropnenol at 58 for the edible portion of fish and shellfish consumed by Americans. This estimate is based on measured steady-state bioconcentration studies in goldfish (Carassius auratus), bluegill (Lepomis macrochirus), eastern oyster (Crassostrea virginica), and sheepshead minnow (Cyprinodon variegatus).

Inhalation and dermal exposure data for the general population are not available (U.S. EPA, 1979). These routes of exposure are more likely to occur occupationally.

Total body exposures, based on reported urine levels of pentachlorophenol, appear to be in the range of 10-17 µg/person/day for the general population and 1500-4400 µg/person/day for occupational exposures (U.S. EPA, 1979). These values may be

due not only to direct exposure to pentachlorophenol, but also to exposure to hexachlorobenzene (pesticide, fungicide) and lindane (pesticide), which are degraded in part to pentachlorophenol (Yang, et al. 1975; Lui and Sweeney, 1975; Mehendale, et al. 1975; Koss and Koransky, 1978; Karapally, et al. 1973; Engst, et al. 1976).

III. PHARMACOKINETICS

A. Absorption

The half-life for absorption in humans after oral ingestion of pentachlorophenol is 1.3 ± 0.4 hr. In humans, a peak plasma concentration of 0.248 mg/l was observed four hours after ingestion of a 0.1 mg/kg dose (Braun, et al. 1978). Absorption in rats is similar to that found in humans (Braun, et al. 1977).

Pentachlorophenol is readily absorbed through the skin as indicated by its lethality after dermal exposure (Deichmann, et al. 1942; Armstrong, et al. 1969).

B. Distribution

In humans (fatal pentachlorophenol intoxication) and in rats (non-lethal exposure), the highest levels of pentachlorophenol are found in liver, kidney, and blood, with the lowest levels in brain, spleen, and fat (Cretney, 1976; Armstrong, et al. 1969; Braun, et al. 1977; Larsen, et al. 1975).

C. Metabolism

In four male volunteers ingesting 0.1 mg pentachlorophenol/kg, approximately 74 percent of the dose was eliminated in the urine as pentachlorophenol (PCP) and 12 percent as PCP glucuronide; four percent was eliminated in feces as pentachloro-

phenol and PCP glucuronide (Braun, et al. 1978). Rats excrete 75 percent of administered pentachlorophenol as the unchanged PCP, 16 percent as tetrachlorohydroquinone, and nine percent as PCP glucuronide (Braun, et al. 1977). In another study (Ahlborg, 1978), trichloro-p-hydroquinone was found as an additional metabolite of pentachlorophenol in rats. Mice also metabolize pentachlorophenol to tetrachlorohydroquinone (Jakobson and Yllner, 1971).

D. Excretion

In humans and in experimental animals, the primary mode of excretion for pentachlorophenol is in the urine (Diechmann, et al. 1942; Braun, et al. 1977, 1978; Larsen, et al. 1975; Jakobson and Yllner, 1971).

In humans, the plasma pentachlorophenol half-life is 30.2 ± 4.0 hours. The half-lives for elimination of pentachlorophenol and PCP glucuronide from urine are 33.1 ± 4.5 and 12.7 ± 5.4 hours, respectively (Braun, et al. 1978). Elimination of pentachlorophenol by the rat is similar to elimination by humans (Braun, et al. 1977).

The available literature indicates that pentachlorophenol does not accumulate in body tissues to any significant extent (U.S. EPA, 1979). Long term, low level tissue binding has not been adequately studied.

IV. EFFECTS

A. Carcinogenicity

Pentachlorophenol has not shown evidence of carcinogenicity. Pentachlorophenol did not promote papillomas or carcinomas when applied repeatedly to the skin at high concentra-

tions after initiation with dimethylbenzanthracene (Boutwell and Bosch, 1959). Mice receiving commercial pentachlorophenol in the diet throughout their lifespans (about 18 months) did not have a significant incidence of tumors (Innes, et al. 1969). Pentachlorophenol, with low levels of nonphenolic contaminants, was non-carcinogenic when fed to rats for 22 to 24 months (Schwetz, et al. 1978).

B. Mutagenicity

Pentachlorophenol has been shown to be mutagenic in a few test systems. Recrystallized pentachlorophenol increased the frequency of mutations and mitotic gene conversion in Saccharomyces cerevisiae when used at a level (400 mg/l) which resulted in a 59 percent survival rate of test organisms (Fahrig, et al. 1978). Four of the 473 offspring of female mice injected with a single high dose of pure pentachlorophenol during gestation were reported to have changes in hair coat color (spots) of genetic significance (Fahrig, et al. 1978).

No mutagenic activity was detected in male germ cells of Drosophila (Vogel and Chandler, 1974), in the mouse host-mediated assay, in in vitro spot tests (Buselmaier, et al. 1973), or in histidine-required mutants of Salmonella typhimurium (Anderson, et al. 1972).

C. Teratogenicity

Information suggesting pentachlorophenol is a human teratogen was not encountered. Pentachlorophenol of both commercial and purified grades produced fetal anomalies in rats at levels considered to be toxic either to the maternal rat or

to the fetus (Larsen, et al. 1975; Schwetz, et al. 1974; 1978). Abnormalities included subcutaneous edema, dilated ureters, delayed ossification of the skull, skeletal anomalies, dwarfism, exencephaly, macropthalmia, and taillessness.

D. Other Reproductive Effects

In a study in which male and female rats were fed 3 or 30 mg/kg pentachlorophenol continuously starting 62 days before mating, no adverse effects were observed at the 3 mg/kg level. At 30 mg/kg, the following indices were decreased: maternal body weight; percent liveborn pups; 7., 14, 21 day survival; 1, 7, 14, 21 day body weight-pups; 7, 14, 21 day litter size. Selected abnormalities were also seen at this dose.(Schwetz, et al. 1978).

E. Chronic Toxicity

Adverse health effects have been minimal in workers chronically exposed to pentachlorophenol (Klemmer, 1972; Takahashi, et al. 1976). Increased levels of serum enzymes SGOT, SGPT, and LDH, and elevated levels of total bilirubin and creatine phosphokinase were noted, but all levels were still within normal limits. A significantly higher prevalence of gamma mobility C-reactive protein (CRP) was detected in the sera of chronically exposed workers. CRP levels are often elevated in acute states of various inflammatory disorders or tissue damage (Takahashi, et al. 1976). A chronic health effect which has been associated with human exposure to certain types of commercial PCP is chloracne (Baader and Bauer, 1951; Nomura, 1953). Chloracne could have resulted from impurities in the pentachlorophenol; commercial PCP containing high levels of chlorodioxins produced chloracne in the rabbit ear test, while pure pentachlorophenol or penta-

chlorophenol with reduced dioxin content did not (Johnson, et al. 1973).

Chronic intoxication in humans results from relatively high levels of continuous exposure. Symptoms include muscle weakness, headache, anorexia, abdominal pain, and weight loss in addition to skin, eye, and respiratory tract irritation (U.S. EPA, 1979).

Rats fed pentachlorophenol containing low levels of nonphenolic contaminants at daily levels of 1 to 30 mg/kg for eight months (Goldstein, et al. 1977) and 22 to 24 months (Schwetz, et al. 1978) had decreased body weight gains at dosage levels of 30 and 10 mg/kg, respectively. In the 22 to 24 month study, the 30 mg/kg dose resulted in increased serum enzyme SGPT levels and increased specific gravity of the urine.

F. Other Relevant Information

Pentachlorophenol is a strong uncoupler of oxidative phosphorylation (Weinbach and Garbus, 1965; Mitsuda, et al. 1963).

V. AQUATIC TOXICITY

A. Acute Toxicity

The results of 38 freshwater flow-through bioassays reveal a range of 96-hour LC_{50} values of from 63 µg/l for the sockeye salmon (Oncorhynchus nerka) (Webb and Brett, 1973) to 340 µg/l for the fathead minnow (Pimephales promelas) (Ruesink and Smith, 1975). In 19 static assays, LC_{50} values ranged from 37 µg/l for the coho salmon (O. kisutch) to 600 µg/l for the fathead minnow. Five species of salmonids were more sensitive than 4 other species of minnows or centrachids. Freshwater invertebrates displayed LC_{50} values ranging from 310 µg/l to 1,400

µg/l for the tubificid worm (Tubifex tubifex) and were affected by increasing the PH from 7.5 to 9.5. The acute toxicity of pentachlorophenol to saltwater fish ranged from 38 µg/l in a 96-hour static pinfish (prolarvae) (Lagodon rhomboides) assay (Borthwick and Schimmel, 1978) to 442 µg/l for juvenile sheepshead minnows (Cyprinodon variegatus) (Parrish, et al. 1978). For three marine invertebrate species tested, LC_{50} values ranged from 40 to 5,600 µg/l, with the eastern oyster (Crassostrea virginica) being the most sensitive marine invertebrate.

B. Chronic Toxicity

Freshwater chronic studies for fish or invertebrates were not available. A life-cycle chronic test of 151 days in the marine sheepshead minnow produced a chronic value of 64 µg/l (Parrish, et al. 1978). Data for marine invertebrates was not available (U.S. EPA, 1979).

C. Plant Effects

For freshwater plants, the lowest effective concentration was 7.5 µg/l, which resulted in the total destruction of chlorophyll in the alga Chlorella pyrenoidosa after 72 hours. A drastic decrease in cell numbers of the marine alga Monochrysis lutheri was observed after 12 days of exposure to 293 µg/l (Woelke, 1965), and 50 percent inactivation of photosynthesis was seen in kelp (Macrocystis pyrifera) exposed for 4 days to 300 µg/l (Clendenning and North, 1960).

D. Residues

Equilibrium levels of PCP in water and tissues of aquatic organisms are attainable within four days; and when previously exposed marine eastern oysters (Crassostrea virginica)

or freshwater bluegills (Lepomis macrochirus) were held in PCP-free water, a rapid loss of PCP from the organism occurred (Schimmel, et al. 1978; Pruitt, et al. 1977). Bioconcentration factors in marine organisms ranged from 0.26 for the juvenile brown shrimp (Penaeus aztecus) to 78 for the eastern oyster. In freshwater fish, bioconcentration factors of 1,000 for the whole body of the goldfish (Carassius auratus) and of 13 for the muscle tissue of the bluegill have been reported (Kobayashi and Akitake, 1975; Pruitt, et al. 1977).

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The U.S. EPA (1979) draft criterion for pentachlorophenol in ambient water is 680 ug/l.

The maximum air concentration established by the American Industrial Hygiene Association (1970) is 0.5 mg pentachlorophenol or 0.5 mg sodium pentachlorophenate/m^3 for an 8-hour exposure (TLV). The code of Federal Regulations 21, part 121, paragraph 121:2556 allows up to 50 ppm pentachlorophenol in treated wood which will come in contact with food.

A NOEL in drinking water of 0.021 mg pentachlorophenol/l is suggested by the National Research Council (1977), based on a NOEL of 3 mg/kg in 90 day and 8 month rat studies and an uncertainty factor of 1,000.

B. Aquatic

The draft criterion to protect marine life is 6.2 µg/l as a 24-hour average, not to exceed 14 µg/l at any time. The draft criterion to protect marine life is 3.7 µg/l for a 24-hour average, not to exceed 8.5 µg/l at any time (U.S. EPA, 1979).

PENTACHLOROPHENOL

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No. 144

Phenol

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

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PHENOL

SUMMARY

Insufficient data exist to indicate that phenol is a carcinogenic agent. In skin painting studies, phenol appears to function primarily as a nonspecific irritant. Information on the mutagenicity of phenol is equivocal. Phenol does not appear to be teratogenic. Chronic exposure to phenol at relatively high levels causes liver damage in humans and animals, and kidney damage in animals. Exposure to acutely toxic levels of phenol causes CNS depression.

The toxic effects of phenol have been extensively examined in freshwater organisms by acute studies in 13 fish and 13 invertebrate species. Considerable interspecies and intra species variation were described, with acute values ranging from 5,020 to 780,000 ug/l. Only three marine species were examined in acute tests, and LC_{50} values ranged from 5,200 to 58,250 ug/l.

PHENOL

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Phenol (U.S. EPA, 1979).

Phenol (C_6H_5OH; molecular weight 94.11) is a clear, colorless (light pink when impurities are present) hygroscopic, crystalline solid at 25° C with the following physical and chemical properties (Manufacturing Chemist Assoc., 1974; Kirk and Othmer, 1963; Weast, 1974).

Melting Point	43° C
Boiling Point	182° C at 760 mm Hg
Flash Point	open cup 85° C closed cup 79° C
Vapor Pressure	0.35 mm Hg at 25° C
Solubility	Water: 6.7 g/100 ml at 16° C and is soluble at all proportions at 66° C. Also soluble in ether, alcohol, acetic acid, glycerol, liquid sulfur dioxide, benzene, and oils.

Industrial capacity for production is 1.44 to 10^6 tons per year (Chem. Eng. News, 1975). About 90 percent of the phenol produced is used in the production of phenolic resins, caprolactam, bisphenol-A, alkylphenols, and adipic acid (Chemical Profiles, 1972).

Phenol may be biochemically hydroxylated to ortho- and para-dihydroxybenzenes and readily oxidized to the corresponding benzoquinones. These may in turn react with numerous components of industrial waters or sewage such as mercaptans, amines, or the -SH or -NH groups of proteins (Stom, 1975). When ambient water containing phenols is chlorinated, various chlorinated phenols may be produced in sufficient

quantities to produce an objectionable taste and odor (Aly, 1968; Barnhart and Campbell, 1972; Jolley, 1973; Jolley, et al. 1975).

II. EXPOSURE

A. Water

There have been no market basket surveys of free and conjugated phenols with which to estimate the average daily dietary intake of phenols. The National Organic Monitoring Survey (U.S. EPA, 1977) reported finding unspecified concentrations of phenol in 2 out of 110 raw water supplies. The Survey found no phenol in any finished water supplies. The National Commission on Water Quality (1975) reported an annual mean concentration of 1.5 ug phenol/l in raw water from the lower Mississippi River.

B. Food

Phenol is produced endogenously in the mammalian intestinal tract through microbial metabolism (Harborne, 1964) and free and conjugated phenol is a normal constituent of animal matter (U.S. EPA, 1979). Phenol concentrations of 7 mg/kg in smoked summer sausage and 28.6 mg/kg in smoked pork belly have been reported (Lustre and Issenberg, 1970). Several mouthwashes and lozenges contain phenol in amounts of up to 32.5 mg total phenol/lozenge.

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for phenol to be 2.3 in the edible portions of fish and shellfish consumed by Americans. This estimate is based on the octanol/water partition coefficient of phenol.

C. Inhalation

The inhalation of phenol vapor appears to be largely restricted to the occupational environment (U.S. EPA, 1979). Dermal exposures can be from a number of medicinal preparations for skin application (lotions, powders, ointments) containing up to 4.75 percent phenol, or from certain feminine hygiene products, and hemorrhoidal products (U.S. EPA, 1979).

III. PHARMACOKINETICS

A. Absorption

Phenol is readily absorbed by all routes. This is illustrated by the fact that acutely toxic doses of phenol can produce symptoms within minutes of administration regardless of the route of entry (U.S. EPA, 1979). Sixty to 80 percent of inhaled phenol is retained in the lungs. Piotrowski (1971) found that phenol vapor could be readily absorbed by intact human skin. The rate of dermal absorption for phenol vapor can be represented by the formula $A=(0.35)C$, when A is the amount of phenol absorbed in mg/hour and C is the phenol concentration in mg/m^3 (Piotrowski, 1971; recalculation of data of Ohtsuji and Ikeda, 1972 by U.S. EPA, 1979).

B. Distribution

Free and conjugated phenol appear to be normal trace constituents in humans and other mammals (Harborne, 1964). Values reported for free and conjugated phenol in normal human blood vary greatly due in part to the specificity of the analytical methods used in and in part to the

amount of the dietary protein which increases urinary phenol excretion. Recent values in normal human blood are between 0.04 to 0.56 mg/l for the free phenol and 1.06 to 5.18 mg/l for conjugated phenols (Dirmikis and Darbre, 1974). For the total phenol (free and conjugated) a range between 2 and 18 mg/l has been reported (Van Haaften and Sie, 1965).

Upon absorption, phenol is rapidly distributed to all organ systems, followed by relatively rapid metabolism and excretion. Within 15 minutes of an oral dose, the highest concentrations are found in the liver, followed by heart, kidneys, lungs, brain and blood (Deichmann, 1944).

C. Metabolism

The major metabolites of phenol are sulfate and glucuronic acid conjugates of phenol and 1,4-dihydroxybenzene. There are, however, species differences in the excretion pattern of these metabolites (Capel, et al. 1972). The cat, which is sensitive to phenol, in addition to sulfate conjugated phenols, excretes also, as a major metabolite, 1,4-dihydroxybenzene (Miller, et al. 1976). The metabolic pattern is also dose dependent. Other agents, which are normally metabolized to phenol, such as benzene or phenylsalicylate, produce increased urinary excretion of phenol metabolites (Kociba, et al. 1976).

D. Excretion

In humans and in all mammals that have been tested, nearly all of the phenol and its metabolites are excreted in the urine within 24 hours (U.S. EPA, 1979; Piotrowski, 1971; Deichmann and Keplinger, 1963). Reported normal background

values for human urinary phenol range from 1.5 to 5 mg/l (Fishbeck, et al. 1975; U.S. EPA, 1979). Urinary excretion levels of phenol metabolites in workers exposed to phenylsalicylate ranged from 150 to 1,371 mg/l. Upon ingestion of eight chloraseptic lozenges at the recommended dosing schedule, the total phenol and the free phenol concentrations in the urine peaked at 270 and 10 mg/l, respectively. When dogs were fed 125 mg phenylsalicylate/kg/day for 41 days, the peak urinary phenol concentration was 6,144 mg/l and the treatment was not associated with ill effects (Kociba, et al. 1976). The half-life of phenol in man is approximately 3.5 hours (U.S. EPA, 1979).

IV. EFFECTS

A. Carcinogenicity

There is no convincing evidence that phenol acts as a carcinogen, particularly at concentrations within normal physiologic limits. Phenol appears to function primarily as a nonspecific irritant (NIOSH, 1976). Only one case of human cancer associated with exposure to phenol was found in the literature. A 72-year old man who had applied a salve of phenol and ergot to his back daily for 20 years developed an invasive squammous cell epithelioma (Stevens and Callaway, 1940).

Phenol produced papillomas but not carcinomas when applied to the skin of some strains of mice. Phenol has carcinogenic activity when applied repeatedly to the skin of a specially bred strain of Sutter mice at concentrations which produce repeated skin damage (Boutwell and Bosch, 1959; Sala-

man and Glendenning, 1956). Phenol promotes skin cancer in mice when repeatedly applied after initiation with known carcinogens (Boutwell and Bosch, 1959; Salaman and Glendenning, 1956; Van Duuren, et al. 1971). Tumorigenesis is highest at dose levels of phenol which have some sclerosing activity. Phenol has no cocarcinogenic activity when applied simultaneously and repeatedly with benzo(a)pyrene to mouse skin (Van Duuren, et al. 1973).

B. Mutagenicity

Phenol was found to be mutagenic in Drosphila (Hadorn and Niggli, 1946) and also reported to be nonmutagenic for Neurospora (Dickey, et al. 1949). Phenol produced back mutations in E. coli from streptomycin dependence to non-dependence at phenol concentrations high enough that the survival of bacteria was only 0.5 to 1.7 percent (Demerec, et al. 1951).

C. Teratogenicity

Studies dealing directly with teratogenicity were not reported in the U.S. EPA (1979) or NIOSH (1976) documents. In a study, not designed specifically as a teratogenicity study, rats were given phenol at concentrations of 100 to 12,000 mg/l in their drinking water over three to five generations. Specific teratogenic effects were not noted (Heller and Pursell, 1938).

D. Other Reproductive Effects

In the study mentioned under teratogenicity, higher concentrations of phenol in the drinking water (7,000 mg/l) produced stunted growth in the young, death of the offspring

at birth (10,000 mg/l), and failure to reproduce (12,000 mg/l) (Heller and Pursell, 1938).

E. Chronic Toxicity

Repeated exposures to phenol at high concentrations have resulted in chronic liver damage in humans (Merliss, 1972). In unpublished studies by Dow Chemical Company (1976), rats received 135 doses of 100 mg phenol/kg or 50 mg phenol/kg by gavage over a six month period. The growth of the rats was comparable to that of controls. Very slight liver changes and slight to moderate kidney damage were seen at the higher dose of phenol. The lower dose of phenol produced only slight kidney damage.

Rats given phenol in their drinking water at 800, 1,200, 1,600, 2,000, and 2,400 mg/l had corresponding average intakes of 21, 30, 49, 56, and 55 mg phenol per rat per day based on actual water consumption data. The rats at the three lower dosage levels showed no overt symptoms of toxicity. The weight gain of the rats at the two highest dose levels was depressed (Deichmann and Oesper, 1940).

F. Other Relevant Information

The primary effect of exposure to acutely toxic levels of phenol is CNS depression. Significant evidence could not be found to support the occurrence of synergistic or antagonistic actions of phenol with other compounds in mammals (U.S. EPA, 1979).

V. AQUATIC TOXICITY

A. Acute Toxicity

Acute toxicity data for phenol display a wide range of interspecific variability and intraspecific sensitivity. The range of LC_{50} values for 13 species of freshwater fish is 5,020 ug/l for the rainbow trout (Salmo gairdneri) to 200,000 ug/l for the goldfish (Carassius auratus) (Cairns, et al. 1978). Several studies have indicated an inverse relationship between survival time and temperature for rainbow trout, golden shiner (Notemigonius crysoleueus) (U.S. EPA, 1979). Similar intraspecific sensitivity and interspecific variability was demonstrated by bioassays with freshwater invertebrates as test organisms. The cladocerans, Daphnia magna and D. longispina, displayed the greatest sensitivity to phenol with LC_{50} values as low as 7,000 ug/l reported. The freshwater clam, Sphaerium corneum, was the most resistant species with an LC_{50} value of 780,000 ug/l (U.S. EPA, 1979).

Data for the acute toxicity of phenol to marine organisms is not nearly as extensive as that for freshwater species. For marine fish, LC_{50} values of 5,200 and 6,014 ug/l were obtained for rainbow trout in saline waters and mountain bass (Kuhlia sandvicensis), respectively (U.S. EPA, 1979). Eastern oyster embryos (Crassostrea virginica) and hardclam embryos (Mercenaria mercenaria) were much more resistant with LC_{50} values of 58,250 and 52,630 ug/l, respectively (Davis and Hidu, 1969).

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B. Chronic

Data for the chronic effects of phenol on freshwater fish are not available. In a life cycle chronic test, a chronic value of 3,074 µg/l was obtained for the freshwater cladoceran, Daphnia magna (U.S. EPA, 1978). Chronic data for marine organisms were not available.

C. Plant Effects

Plants are relatively insensitive to phenol exposure with effective concentrations ranging from 20,000 to 1,504,000 µg/l for three species of algae, one species of diatom, and duckweed. Marine plants species have not been examined for toxic effects of phenol.

D. Residues

Measured bioconcentration factors of 1.2 to 2.3 have been determined for goldfish (Kobayashi, et al. 1976; Kobayashi and Akitake, 1975). Bioconcentration factors have not been determined for freshwater invertebrates or plants, or for any marine species.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

On the basis of chronic toxicity data for rats and an uncertainity factor of 500, the U.S. EPA (1979) has derived a draft criterion of 3.4 mg/l for phenol in ambient water corresponding to the calculated acceptable daily intake

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of 0.7 mg. The draft criterion for phenol is 1.0 ug/l in those instances where chlorination of phenol may take place during water purification processes.

The 1974 Federal standard and the ACGIH (1977) recommendation for phenol in air in the workplace is 19 mg/m^3 (5 ppm) as a time-weighted average.

The NIOSH (1976) criterion for a recommended standard for occupational exposure to phenol is 20 mg/m^3 in air as a time weighted average for up to a 10-hour work day and a 40-hour work week, with a ceiling concentration of 60 mg/m^3 for any 15-minute sampling period.

The U.S. EPA interim drinking water limit for phenol is 1 ug/l, which is largely an organoleptic standard based on the objectionable taste and odor produced by chlorinated phenols. In response to a phenol spill in southern Wisconsin, the U.S. EPA proposed on November 26, 1974 an emergency standard of 0.1 mg phenol/l as being temporarily acceptable for human consumption.

3. Aquatic

The draft criterion for protecting freshwater organisms is 600 ug/l, not to exceed 3,400 ug/l. No criterion for marine organisms was derived (U.S. EPA, 1979).

PHENOL

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No. 145

Phorate

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

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PHORATE

Summary

Phorate is an organophosphorous insecticide used on a variety of crops, mainly in south-central states. Phorate is readily absorbed through inhalation and skin contact and is highly toxic to humans and other animals. Primarily, it affects the central and peripheral nervous systems by inhibiting cholinesterase activity. Information concerning carcinogenic and mutagenic effects was not located in the available literature. The threshold limit value for phorate is 50 $\mu g/m^3$, based on dermal contact. Additionally, phorate has been classified for restrictive use by the U.S. EPA.

Although phorate is highly toxic to certain aquatic organisms, no apparent adverse effects have been observed in the aquatic environment.

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I. INTRODUCTION

Phorate is a highly toxic organophosphorous insecticide used on a variety of agricultural crops. It was introduced in 1954 by the American Cyanamid Co. under the trade name Thimet® (Martin and Worthing, 1974). Phorate is prepared by the reaction of phosphorous pentasulfide with ethanol, formaldehyde, and ethyl mercapton. Production in the U.S. totaled 3400 tonnes in 1977 (NAS, 1977). Virtually all of the phorate is used on root and field cropsoils to control sucking insects and nematodes (NAS, 1975). Phorate is slightly soluble in water and hydrolyzes in moisture. It has an overall degradation rate constant of 0.02/day and a bioconcentration factor of 5.2. Other properties are listed in Table 1.

II. EXPOSURE

A. Water

Phorate is produced in the United States by the American Cyanamid Co. at Hannibal, Mo. (SRI, 1977). Available information on an annual U.S. production shows that 1900 tonnes were produced in 1971, 3600 tonnes in 1974, and 3400 tonnes in 1977 (NAS, 1975, 1977). Berg, et al. (1972) noted an application rate of 1 pound of actual material per acre (1.1 kg/ha; in this case, to control corn borers). Application rates vary according to use.

Phorate has found increasing use on croplands in the south-central states to protect cotton, hops, alfalfa, barley, sorghum, peanuts, sugar beets, sugar cane, potatoes, rice, and tomatoes. Only small amounts are used in the southeastern and northeastern U.S. American Cyanamid Co. reported that phorate may fill the void left by the removal from the market of chlorinated hydrocarbons and projected a strong demand for phorate in the corn rootworm market (Berg, et al. 1977).

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TABLE 1. PHYSICAL AND CHEMICAL PROPERTIES OF PHORATE

Synonyms: O,O-diethyl-S-(ethylthiomethyl)phosphorodithioate;
O,O-diethyl-S-ethylmercaptomethyl dithiophosphate;
THIMET American Cyanamid (3911): timet (USSR);
CAS Registry No. (298-02-2); Dranutox; Rampart; Vergfru

Structural Formula: $(C_2H_5O)_2(P{=}S)SCH_2SC_2H_5$

Molecular Weight: 260.4

Description: Clear liquid
Miscible with: CCl_4, dioxan, vegetable oils, xylene, alcohols, ethers, esters

Soil Attenuation: K_d approx. 5×10^2; $K_{oc} = 3199$

Specific Gravity and/or Density: $d^{25} = 1.167$

Melting and/or Boiling Points: bp 118 to 120°C at 0.8 mm
mp less than -15°C

Stability: Stable at room temperature
Hydrolyzed in the presence of moisture
Overall degradation rate constant (0.02/day)

Soil half-life: 1-4 weeks
Bacterial/Hydrolysis: constant = $8 \times 10^{-4} hr^{-1}$

Solubility (water): 50 ppm at room temp.
$\frac{\text{sediment}}{H_2O} : \frac{4.5}{1}$

Vapor Pressure: 8.4×10^{-4} mm Hg at 20°C

Bioconcentration Factor (BCF) and/or
Octanol/water partition coefficient (K_{ow}): $K_{ow} = 18$
BCF = 5.2

Source: Martin and Worthing, 1974; Fairchild, 1977; Windholz, 1976; U.S. EPA, 1980

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Little information was found on phorate production processes. Lawless, et al. (1977) noted that in the production, crude phorate was washed and filtered. No information was given on the treatment of the waste water or filter cake associated with this process. No information on waste sludge or landfill disposal was found in the available literature.

Phorate can enter water by runoff or by ground water drainage after application. Phorate is relatively stable in ground water. Only 10 percent decomposition was estimated in a river environment in 5 days (50 to 250 mile transport; 80-400 km). Also, estimates show that less than 90 percent decomposition per year occurs in a lake environment (U.S. EPA, 1980). There are no estimates on the amount of phorate entering the environment or on the levels of phorate in ambient water. Menzie (1974) noted that phorate decomposes to phorate sulfoxide and phorate sulfone and the sulfoxide and sulfone of the oxygen analog.

Walter-Echols and Lichtenstein (1977) showed that some oxidation products of phorate (phorate sulfoxide) reduce to phorate in lake mud under certain conditions. Using a flooded phorate sulfoxide-treated loam soil, they noticed the production of only small amounts of phorate. After lake mud was added, the reduction of phorate sulfoxide to phorate increased dramatically and, after two weeks' incubation, accounted for 44 percent of the recovered residues. They related the reduction process to the activity of microorganisms in an environment of organic nutrients.

B. Food

Information available in the open literature does not quantify the amount of phorate detected on foods. In a study reported by Menzie (1974), phorate was applied to bermuda grass and corn at the rate of 2 pounds per

acre (2.2 kg/ha). Fourteen days after treatment, less than 1 ppm phorate residue was noted on the corn; after 21 days less than 1 ppm was found on bermuda grass.

C. Inhalation and Dermal

Data are not available indicating the number of people subject to inhalation or dermal exposure to phorate. The primary human exposure would appear to occur during production and application. The U.S. EPA (1976) listed by occupational group the frequency of illness caused by exposure to organophosphorous pesticides. Of 1157 reported cases, most illnesses occurred among ground applicators (229) and mixer/loaders (142); the lack of, or refusal to use, safety equipment was a major factor of this contamination. Other groups affected were gardeners (101), field workers exposed to pesticide residues (117), nursery and greenhouse workers (75), soil fumigators in agriculture (29), equipment cleaners and mechanics (28), tractor drivers and irrigators (23), workers exposed to pesticide drift (22), pilots (crop dusters) (17), and flaggers for aerial application (6). Most illnesses were a result of carelessness, lack of knowledge of the hazards, and/or lack of safety equipment. Under dry, hot conditions, workers tended not to wear protective clothing. Such conditions also tended to increase pesticide levels and dust on the workers.

III. PHARMACOKINETICS

A. Absorption

Newell and Dilley (1978) exposed four different groups of rats to phorate via four routes of administration. They compared LD_{50} and LC_{50} values and found that inhalation was the most toxic route, followed, in decreasing order, by intravenous, oral, and dermal routes. The phorate aero-

sol generated in the laboratory had a particle size range of 0.3-3.0 μm diameter, a size small enough to enter the gas exchange regions of the lung.

Young, et al. (1979) reported on two occupational exposure incidents that suggested absorption in the lungs was the most effective route of entry. In both cases, the individuals wore protective clothing, goggles, and respirators while working in the dust house where technical grade phorate was produced. Gas chromatographic analyses of air samples from the dust house showed phorate levels ranging from 0.7 to 14.6 mg/m^3. No estimate of particle size was reported by the authors.

B. Distribution

Phorate would be expected to distribute in the body like organophosphorous pesticides of similar solubility. A report by Pugh and Forest (1975) described the distribution in calves exposed to phorate in a manger containing 1200 ppm. Phorate concentrations in the liver ranged from 0.004-0.26 ppm; in the kidney, 0.002-0.021 ppm; and in the brain, 0.025-0.19 ppm.

C. Metabolism

The major phorate metabolites found in blood after oral administration to rats are phorate sulfoxide, phorate sulfone, and phoratoxon sulfone (NAS, 1977). Bowman and Casida (1958) showed that phorate hydrolyzes in rats to produce urinary diethylphosphorodithioic acid, diethylphosphorothioic acid, and diethylphosphoric acid. Oxidative metabolites are not found as components of excretory products of animals treated with phorate (NAS, 1977). However, DuBois, et al. (1950) showed that in rat liver slices, phorate was converted to its oxidative products.

D. Excretion

The previous section notes that phorate is eliminated primarily through the urinary system.

IV. EFFECTS

A. Carcinogenicity and Mutagenicity

Pertinent data could not be located in the available literature on the carcinogenicity or mutagenicity of phorate. Formaldehyde, a suspected carcinogen, and other contaminants may be present in technical grade phorate.

B. Teratogenicity

In a study described in the absorption section of this report, Newell and Dilley (1978) did not find dose-related teratogenesis in rats exposed to phorate via inhalation, intravenous, dermal, or oral routes. In the chick embryo test, Richert and Prahlad (1972) injected 1.5 or 2.0 ppm in a peanut oil medium into eggs on the tenth day of incubation. Controls received only peanut oil. Hatchability of the eggs decreased in a dose-dependent manner. Malformations were produced, but these did not seem to be dose-related. The relevance of these studies to mammalian teratology is unclear (NAS, 1977).

C. Other Reproductive Effects

In a study in which CFI mice were fed diets containing 98.7 percent phorate at 0.6, 1.5, and 3.0 ppm, the no-adverse-effect level for reproductive performance was 1.5 ppm (NAS, 1977).

D. Chronic Toxicity and Other Relevant Information

Pertinent data on chronic toxicity could not be located in the available literature. Several subchronic studies have been reported. In subchronic feeding studies of 1, 5, and 25 ppm phorate for 28 days, cholinesterase in the 1 ppm group was not decreased (Tusing, 1955). In a second rat study, Tusing (1956) fed groups of 50 males and females 92 percent phorate for 13 weeks at 0.22, 0.66, 2.0, 6.0, 12.0, and 18.0 ppm. He noted a no-adverse-effect dosage at 0.66 ppm.

Tusing (1956) fed three dogs 92 percent phorate at 0.01, 0.05, 0.25 and 1.24 mg/kg 6 days per week for 13-15 weeks. The no-adverse-effect dosage was judged to be 0.01 mg/kg; even at this level, a very slight decrease in plasma cholinesterase resulted. Higher dosages caused significant depression of cholinesterase, culminating in death at the two highest dosages.

Rat feeding studies showed higher subchronic toxicities on phorate oxidative metabolites than on phorate, according to Rombunski, et al. (1958). Others have also noted that phorate metabolites are more potent cholinesterase inhibitors than phorate (Curry, et al. 1961).

Young, et al. (1979) reported on acute exposures to high levels of phorate (up to 14.6 mg/m^3) in a production facility (see absorption section). The symptoms accompanying the exposures were confusion, dizziness, nausea, vomiting, pupil constriction, respiratory distress, cardiac arrhythmia, and unconsciousness. Treatment involved a regime of PAM and atropine. According to Gleason (1969), the symptoms produced by a sublethal dose are typical of central and peripheral nervous system toxicity. EPA's accident files contain reports of 21 episodes of poisoning involving phorate for 1971-1973. Eleven were agriculturally related. There are no controlled studies in humans from which no-adverse-effect dosages could be derived.

For humans, the lowest published lethal (LD_{Lo}) value is estimated to be 5 mg/kg. The following studies list acute phorate toxicity levels for human and nonhuman species, reported by Fairchild (1977):

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Species	Exposure	LD_{50} (mg/kg)
Rat	Oral	1.1
Rat	Skin	2.5
Rat	Intravenous	1.2
Mouse	Oral	11
Guinea pig	Oral	20
Guinea pig	Skin	20
Duck	Oral	2.55
Duck	Skin	203
Wild Bird	Oral	1

V. AQUATIC TOXICITY

A. Acute and Chronic Toxicity

Phorate is highly toxic to certain species of fish, crustaceans, and terrestrial wildlife (NAS, 1977). NAS noted that there were no reported killings of these species in the environment.

B. Plant Effects and Residues

Pertinent data could not be located in the available literature.

VI. EXISTING GUIDELINES

A. Human

The threshold limit value for phorate is 50 $\mu g/m^3$, based on skin contact (Fairchild, 1977). An 8-hour time-weighted average of 50 mg/m^3 was adapted for phorate by the Tennessee Department of Health (Young, et al. 1979). In addition, phorate is classified for restrictive use by the U.S. EPA for liquid formulations containing 65 percent and greater active ingredients. The restriction was influenced by the acute dermal toxicity of phorate and by residue effects on avian species (applicable to foliar applications only).

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B. Aquatic

Pertinent data could not be located in the available literature.

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No. 146

Phthalate Esters

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

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PHTHALATE ESTERS

Summary

Certain phthalates (dimethyl phthalate, diethyl phthalate, mono-2-ethyl-hexyl phthalate and dimethoxyethyl phthalate), have shown mutagenic effects in both bacterial systems and the dominant lethal assay.

All eight phthalates tested by injection in pregnant rats produced teratogenic effects. These effects were not noted when DEHP or dibutyl phthalate were administered orally to pregnant rats. Additional reproductive effects produced include impaired implantation, parturition and decreased fertility in rats. Testicular damage has been reported following intraperitoneal (i.p.) or oral administration of DEHP, or oral administration of dibutyl phthalate. No evidence of carcinogenic effects produced by phthalates is available.

Chronic toxicity includes toxic polyneuritis in workers exposed primarily to dibutyl phthalate. DEHP animal studies show induced liver and kidney changes while dimethyl phthalate induced only kidney effects. Following injection dibutoxyethyl phthalate, di-(2-methoxyethyl) phthalate, and octylisodecyl phthalate have caused damage to the developing chick embryo nervous system.

Toxicity of the phthalate esters to aquatic organisms varies within this group of chemicals. Freshwater organisms have appeared somewhat more sensitive than marine species. The data is insufficient to allow for the drafting of criteria to protect aquatic life for any of the phthalates.

PHTHALATE ESTERS

I. INTRODUCTION

This profile is based primarily on the draft Ambient Water Quality Criteria Document for Phthalate Esters (U.S. EPA, 1979).

The phthalate esters are esters of the benzenedicarboxylic acid ortho form. Esters of the parent compound meta and para forms will not be reviewed in this profile. The phthalate esters are colorless liquids of low volatility, poorly soluble in water and soluble in organic solvents and oils. Some physical and chemical properties of the phthalate esters are indicated in Table 1 on the following page (U.S. EPA, 1979).

The phthalate esters are widely used as plasticizers, and through this application are incorporated into wire and cable covering, floor tiles, swimming pool liners, upholstery and seat covers, footwear, and in food and medical packaging materials. Non-plasticizer uses include incorporation into pesticide carriers, cosmetics, fragrances, munitions, industrial oils, and insect repellants (U.S. Int. Trade Commission, 1978). The most current production figure is 6×10^5 tons/year in 1977 (U.S. EPA, 1979).

Phthalate esters are ubiquitous. Monitoring surveys have detected phthalates in soil, air, water, animal and human tissues, and certain vegetation. Some plants and animal tissues may synthesize phthalic acid esters (Peakall, 1975). From <u>in vitro</u> studies indications, certain bacterial flora may be capable of metabolizing phthalates to the monoester form (Englehardt, et al. 1975).

II. EXPOSURE

Phthalate esters appear in all areas of the environment. Environmental release of the phthalates may occur through leaching of plasticizers from polyvinyl chloride (PVC) materials, volatilization of phthalates from PVC

materials, and the incineration of PVC items. Human exposure to phthalates includes contaminated foods and fish, dermal application of phthalates in cosmetics and insect repellants, and parenteral administration by use of PVC blood bags, tubings, and infusion devices (U.S. EPA, 1979).

TABLE 1

PHYSICAL AND CHEMICAL PROPERTIES OF PHTHALATE ESTERS

Phthalate Compounds	Molecular Weight	Specific Gravity	Bp, °C	Percent Solubility in H_2O, g/100 ml
Dimethyl	194.18	1.189 (25/25)	282	0.5
Diethyl	222.23	1.123 (25/4)	296.1	Insoluble
Diallyl	246.27	1.120 (20/20)	290	0.01
Diisobutyl	278.30	1.040	327	Insoluble
Dibutyl	278.34	1.047 (21)	340	0.45 (25°C)
Dimethoxyethyl	282.00	1.171 (20)	190-210	0.85
Dicyclohexyl	330.00	1.200 (25/25)	220-228	Insoluble
Butyl octyl	334.00	—	340	—
Dihexyl	334.00	0.990	—	Insoluble
Butylphthayl butyl glycolate	336.37	1.097 (25/25)	219/5 mm	0.012
Dibutoxyethyl ethyl	366.00	1.063	210	0.03
Di-2-ethylhexyl	391.00	0.985 (20/20)	386.9/5 mm	Insoluble
Diisooctyl	391.00	0.981	239/5 mm	Insoluble
Di-n-octyl	391.00	0.978	220/5 mm	Insoluble
Dinonyl	419.00	0.965	413	Insoluble

Source: U.S. EPA, 1979

Monitoring studies have indicated that most water phthalate concentrations are in the ppm range, approximately 1-2 ug/l (U.S. EPA, 1979). Air levels of phthalates in closed PVC tiled rooms have been reported to be from 0.15 to 0.26 mg/m^3 (Peakall, 1975), while industrial monitoring has measured air levels of phthalates from 1.7 to 66 mg/m^3 (Milkov, et al. 1973). Phthalate levels in various foods have ranged from non-detectable to 82 ppm (Tomita, et al. 1977). Cheeses, milk, fish and shellfish present potential sources of high phthalate intake (U.S. EPA, 1979). Estimates of patient parenteral exposure to di-2-ethylhexyl phthalate (DEHP) during use of PVC medical appliances have indicated approximately 150 mg DEHP exposure from a single hemodialysis course. Through application of certain cosmetics and insect repellants dermal exposure to phthalates is possible (U.S. EPA, 1979).

Using average human fish and shellfish consumption data, the U.S. EPA (1979) has derived the following bioconcentration factors for the edible portions of fish and shellfish consumed by Americans - diethyl phthalate, 270; dibutylphthalate, 1500; DEHP, 95; dimethyl phthalate, 130. DMP, DEP and BBP are based on the steady-state bioconcentrations in bluegills and in fathead minnows for DEHP. A weighted average bioconcentration factor of 26 was calculated for dibutyl phthalate utilizing the octanol water partition coefficient (U.S. EPA, 1979).

III. PHARMACOKINETICS

A. Absorption

The phthalic acid esters and/or their metabolites are readily absorbed from the intestinal tract, the peritoneal cavity, and the lungs (U.S. EPA, 1979). Daniel and Bratt (1974) found that seven days following administration of radiolabelled-DEHP, 42 percent of the dose is recovered in the urine and 57 percent recovered in the feces of rats. Biliary excretion of

orally administered DEHP has been noted by Wallin, et al. (1974). Limited human studies indicate that 2 to 4.5 percent of orally administered DEHP is recovered in the urine within 24 hours (Shaffer, et al. 1945). Lake, et al. (1975) suggest orally administered phthalates are absorbed after metabolic conversion to the monoester form in the gut.

Dermal absorption of DEHP in rabbits has been reported at 16 to 20 percent of the initial dose within three days following administration (Autian, 1973).

B. Distribution

Studies in rats injected with radiolabelled-DEHP have shown that from 60 to 70 percent of the administered dose was detected in the liver and lungs within 2 hours after injection (Daniel and Bratt, 1974). Wadell, et al. (1977) have reported rapid accumulation of radiolabelled-DEHP in the kidney and liver of rats after intravenous (i.v.) injection, followed by rapid excretion into the urine, bile, and intestine. Seven days after i.v. administration of radiolabelled-DEHP to mice, levels of the compound were found preferentially in the lungs and to a lesser extent in the brain, fat, heart, and blood (Autian, 1973).

An examination of tissue samples from two deceased patients, recipients of large volumes of transfused blood, detected DEHP in the spleen, liver, lungs, and abdominal fat (Jaeger and Rubin, 1970). Daniel and Bratt (1974) have suggested phthalates achieve a steady-state concentration, after which the compounds or metabolites are rapidly eliminated by various routes.

Injection of radiolabelled-DEHP and diethyl phthalate in pregnant rats has shown the phthalates may cross the placental barrier (Singh, et al. 1975).

C. Metabolism

Various metabolites of DEHP have been identified following oral feeding of rats (Albro, et al. 1973). These results indicate that DEHP is initially converted from the diester to the monoester, followed by the oxidation of the monoester side chain forming two different alcohols. The alcohols are then oxidized to the corresponding carboxylic acid or ketone. Enzymatic clearance of phthalates to the monoester form may take place in the liver or in the gut (Lake, et al. 1977). This enzymatic conversion has been observed in stored whole blood indicating widespread distribution of this metabolic activity (Rock, et al. 1978).

D. Excretion

Elimination of orally administratered DEHP is virtually completed within four days in the rat (Lake, et al. 1975). Major excretion is through the urine and feces, with biliary excretion increasing the content of DEHP (or metabolites) in the intestine (U.S. EPA, 1979). Schulz and Rubin (1973) have noted a progressive increase in total water soluble metabolites in the first 24 hours following injection of radiolabelled DEHP to rats. Within one hour, eight percent of the DEHP was found in the liver, intestine and urine. After 24 hours, 54.6 percent DEHP was recovered in the intestinal tract, excreted feces and urine, and only 20.5 percent DEHP was recovered in organic extractable form.

The half-life of phthalate elimination from the tissues and total body is short (U.S. EPA, 1979). Biphasic elimination of DEHP from the blood of rats showed half-life values of 9 minutes and 22 minutes, respectively (Schulz and Rubin, 1973).

IV. EFFECTS

A. Carcinogenicity

Pertinent data could not be found in the available literature.

B. Mutagenicity

Testing of several phthalates in the Ames Salmonella assay has shown that diethyl phthalate has some mutagenic activity (Rubin, et al. 1979). Dibutyl, mono-2-ethylhexyl, di-(2-ethylhexyl) and butylbenzyl phthalate all produced negative effects in this test system. Yagi, et al. (1978) have reported mutagenic effects of mono-2-ethylhexyl phthalate in a Bacillus subtillus recombinant assay system.

Results of a dominant lethal assay in mice have indicated DEHP and dimethoxyethyl phthalate showed some mutagenic activity (Singn, et al. 1974).

C. Teratogenicity

The teratogenic effects of a number of phthalate esters (DEHP, dimethyl, dimethoxyethyl, diethyl, diisobutyl, butylcarbobutoxymethyl, and dioctyl phthalates) have been reported in rats (Singh, et al. 1972). Teratogenic effects were not seen following oral administration of DEHP and dibutyl phthalate to rats (Nikonorow, et al. 1973). Damage to the nervous system or developing chick embryos has been produced by injection of dibutoxyethyl phthalate, di-(2-methoxy-ethyl) phthalate, and octyl-isodecyl phthalate (Bower, et al. 1970).

D. Other Reproductive Effects

Effects on implantation and parturition have been observed in pregnant rats injected intraparenteneally with DEHP, dibutyl phthalate, and dimethyl phthalate (Peters and Cook, 1973). A three generation rat reproduction study has indicated decreased fertility following maternal DEHP treatment (Industrial Bio-Test, 1978).

Testicular damage has been reported in rats administered DEHP intraparenteneally or orally. Seth, et al. (1976) found degeneration of the seminiferous tubules and changes in spermatagonia; testicular atrophy and morphological damage was noted in rats fed DEHP or dibutyl phthalate (Carter, et al. 1977).

E. Chronic Toxicity

An increase in toxic polyneuritis has been reported by Milkov, et al. (1973) in workers exposed primarily to dibutyl phthalate. Lesser levels of exposure to dioctyl, diisooctyl, benzylbutyl phthalates, and tricresyl phosphate were also noted. Neurological symptoms have been observed in several phthalate plasticizer workers (Gilioli, 1978). Animal studies have shown central nervous system degeneration and encephalopathy in rats administered large oral or intraperitoneal doses of butylbenzyl phthalate (Mallette and Von Hamm, 1952).

Oral DEHP feeding has produced liver and kidney weight increases in several animal studies (U.S. EPA, 1979). Chronic exposure to transfused blood containing DEHP has produced liver damage in monkeys (Kevy, et al. 1978). Lake, et al. (1975) have produced liver damage in rats by administration of mono-2-ethylhexyl phthalate.

Two-year feeding studies with female rats have shown some kidney effects produced by dimethyl phthalate (Draize, et al. 1948).

F. Other Relevant Information

Several animal studies have demonstrated that DEHP pretreatment of rats resulted in increased hexobarbital sleeping times (Daniel and Bratt, 1974; Rubin and Jaeger, 1973; Swinyard, et al. 1976).

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V. AQUATIC TOXICITY

A. Acute Toxicity

Acute values for freshwater fish were derived from eight 96-hour bioassays for four phthalate esters. LC_{50} values ranged from 730 µg/l for di-n-butyl phthalate in the bluegill sunfish (Lepomis macrochirus) (Mayer and Sanders, 1973) to 98,200 µg/l in diethyl phthalate for the bluegill, Lepomis macrochirus. Butylbenzyl and dimethyl phthalates were intermediate in their toxicity in bluegill assays with LC_{50} values of 43,300 to 49,500 µg/l respectively (U.S. EPA, 1978). The scud, Gammarus pseudolimnaeus, was the most sensitive of freshwater species tested, producing a static 48-hour adjusted LC_{50} value of 765 µg/l (Mayer and Sanders, 1973). In 48-hour static Daphnia magna assays, the adjusted LC_{50} values for butylbenzyl, diethyl dimethyl, and di-n-ethylhexyl phthalates were 92,300, 52,100, 33,000, and 11,100 µg/l, respectively. Among marine fish, juvenile sheepshead minnows, Cyprinodon variegatus, were most susceptible to diethyl phthalate, producing a static 96-hour LC_{50} value of 29,600 µg/l. In similar assays, the LC_{50} values for butylbenzyl and dimethyl phthalate were 445,000 µg/l and 58,000 µg/l respectively. The marine mysid shrimp, Mysidopsis bahia, was tested with diethyl phthalate, and produced a 96-hour LC_{50} value of 7,590 µg/l. LC_{50} values of 9,630 and 73,700 µg/l were reported for butylbenzyl and dimethyl phthalates, respectively, in mysid shrimp assays.

B. Chronic Toxicity

The only chronic studies available are for one species of freshwater fish and one species of freshwater invertebrate (Mehrle and Mayer, 1976; Mayer and Sanders, 1973). A chronic value of 4.2 µg/l was obtained in a rainbow trout, Salmo gairdneri, embryo-larval study of di-(2-ethylhexyl)

phthalate. In Daphnia magna significant reproductive impairment was observed for di-2(-ethylhexyl) phthalate at 3.0 µg/l, the lowest concentration tested. Chronic marine data was not available.

C. Plant Effects

In the freshwater algae, Selenastrum capricornutum, effective concentration ranges of 110 to 130 µg/l; 85,600 to 90,300 µg/l and 39,800 to 42,700 µg/l were obtained for butylbenzyl, diethyl and dimethyl phthalates respectively. Effective concentrations were based on chlorophyll a content and cell number.

D. Residues

Bioconcentration factors have been obtained for five of the phthalates. In the scud, bioconcentration factors of 1400 were reported for di-n-butyl phthalate, and 54,2680 for di-(2-ethylhexyl) phthalate. In the bluegill, bioconcentration factors of 57, 117, and 663 were obtained for dimethyl, diethyl, and butylbenzyl phthalates, respectively. For di-(2-ethylhexyl) phthalate bioconcentration factors were reported from 24 to 150 for the sowbug, Ascellus brevicaudus, 42 to 113 for the rainbow trout, and 155 to 886 for the fathead minnow.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

Based on "no effect" levels observed in chronic feeding studies of rats or dogs, the U.S. EPA calculated acceptable daily intake (ADI) levels for several phthalates, and established recommended water quality criteria

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levels to protect human health for dimethyl phthalate, diethyl phthalate, dibutyl phthalate, and DEHP. These levels are listed in Table 2 (U.S. EPA, 1979)

8. Aquatic

Data are insufficient to derive draft criteria for any of the phthalate esters in either freshwater or marine environments (U.S. EPA, 1979).

TABLE 2

CALCULATED ALLOWABLE DAILY INTAKE IN WATER AND FISH FOR VARIOUS PHTHALATE ESTERS (U.S. EPA, 1979)

Ester	No Effect Dose (mg/kg/day)	Species	Days	ADI** (mg/day)	F***	Recommended Criteria (mg/l)
Dimethyl	1000	Rat	104	700	130	160
Diethyl	625	Dog	52	438	270	60
Dibutyl	18	Dog	52	12.6	26	5
Dicyclohexyl	14	Dog	52	9.8	Not Established	
Methyl phthayl ethyl glycolate	750	Rat	104	525	Not Established	
Ethyl phthayl ethyl glycolate	250	Rat	104	175	Not Established	
Butyl phthayl ethyl glycolate	140	Dog	104	98	Not Established	
Di-2-ethyhexyl	60	Dog	52	42	95	10

**Allowable Daily Intake for 70 kg person (100 safety factor)
***F = Biomagnification factor

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PHTHALATE ESTERS

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No. 147

Phthalic Anhydride

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

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PHTHALIC ANHYDRIDE

Summary

Phthalic anhydride failed to produce carcinogenic effects in rats or mice in a long term National Cancer Institute (NCI) feeding study (7,500 ppm; 15,000 ppm).

Information on the mutagenic effects of phthalic anhydride was not found in the available literature.

The hydrolysis product of phthalic anhydride, phthalic acid, has shown teratogenic effects in the developing chick embryo, but not in any mammalian tests. Phthalic anhydride inhalation at high levels may produce reproductive impairment in male rats.

Chronic occupational exposure to phthalic anhydride has been reported to produce progressive respiratory damage in workers, including marked fibrosis of the lungs.

Data concerning the effects of phthalic anhydride to aquatic organisms was not found in the available literature.

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PHTHALIC ANHYDRIDE

I. INTRODUCTION

This profile is based on the Preliminary Environmental Hazard Assessment of Chlorinated Naphthalenes, Silicones, Fluorocarbons, Benzenepolycarboxylates, and Chlorophenols (U.S. EPA, 1973).

Phthalic anhydride (molecular weight - 148.1) is a white, crystalline solid that melts (sublimes) at 131°C, has a boiling point of 284.5°C, a density of 1.527, and a solubility of 0.62 gms/100 gms water at 25°C (Towle, et al. 1968). This compound is soluble in alcohol and sparingly soluble in ether.

The major uses of phthalic anhydride are in the synthesis of plasticizers, alkyd resins, unsaturated polyester resins, and in the preparation of various classes of chemical dyes (U.S. EPA, 1973).

Production of phthalic anhydride in 1971 was 4×10^5 tons (Blackford, 1970).

Phthalic anhydride is in equilibrium with phthalic acid in aqueous systems. Under dry conditions, phthalic anhydride is relatively stable at ambient temperature (U.S. EPA, 1973). Elevated temperatures will produce oxidative degradation of phthalic anhydride.

Phthalic anhydride is biodegraded by microorganisms (Ribbons and Evans, 1960; Saegar and Tucker, 1973).

II. EXPOSURE

Phthalic anhydride is used in large quantities and therefore has potential for industrial release and environmental contamination. No monitoring data are available to indicate ambient air or water levels of the compound. Fawcett (1970) has determined 40-200 ppm by volume in phthalic anhydride

off-gas process. Phthalic acid wastes have been noted in waste waters from paint and varnish industries (Mirland and Sporykhina, 1968) and alkyd resin plants (Minkovich, 1960).

Human exposure to phthalic anhydride from foods cannot be assessed, due to a lack of monitoring data.

Release of phthalic acid from parenterally-used plastic medical devices (blood bags, plastic tubings, catheters, etc.) may occur since these materials have been treated with phthalate plasticizers; however, no data on this type of release are available (U.S. EPA, 1973).

Bioaccumulation data on phthalic anhydride were not found in the available literature.

III. PHARMACOKINETICS

Specific information on the metabolism, distribution, absorption, or elimination of phthalic anhydride was not found in the available literature.

IV. EFFECTS

A. Carcinogenicity

A long-term carcinogenesis bioassay in rats and mice fed phthalic anhydride (7,500 ppm; 15,000 ppm) has been conducted by the NCI (1979). The results indicate that oral administration of these levels of the compound produced no carcinogenic effects in either of the species used.

B. Mutagenicity

Information on the mutagenic effects of phthalic anhydride was not found in the available literature.

C. Teratogenicity

Phthalic acid was shown to produce an increase in teratogenic effects in the developing chick embryo following injection (Verrett, et al.

1969). Mammalian testing of phthalic acid for teratogenicity failed to show effects in mice (Koehler, et al. 1971).

D. Reproductive Effects

Inhalation exposure of rats to phthalic anhydride at high levels (100-200 mg/l) has been reported to cause testicular changes and impaired reproductive capability (Protsenko, 1970).

E. Chronic Toxicity

Markman and Savinkina (1964) have reported progressive respiratory damage in workers exposed to phthalic anhydride for two years or more. Workers exposed for six years evidenced marked fibrosis of the lungs.

F. Other Relevant Information

Phthalic anhydride has been implicated as a skin sensitizing agent in some individuals exposed for prolonged periods of time (Amer. Ind. Hyg. Assoc., 1967).

V. AQUATIC TOXICITY

Data concerning the effects of phthalic anhydride to aquatic organisms were not found in the available literature.

VI. EXISTING GUIDELINES

The 8-hour, TWA occupational exposure limit established for phthalic anhydride is 1 ppm (ACGIH, 1977).

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PHTHALIC ANHYDRIDE

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No. 148

2-Picoline

Health and Environmental Effects

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2-PICOLINE

Summary

Pertinent data could not be found that defined 2-picoline as a carcinogen or a mutagen. Studies on rats indicated that the structure and composition of the liver and the structure and growth pattern of the skin were disrupted in the offspring of tested rats who were given 157 mg per kg body weight daily during their pregnancy.

2-picoline has been shown to produce biochemical and physical changes in the liver, spleen, bone marrow, and lymph nodes.

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I. INTRODUCTION

2-picoline (alpha-picoline, 2-methylpyridine; CAS No. 109-06-8) is a colorless liquid possessing a strong unpleasant odor. It has the following physical properties:

Formula:	C_6H_7N
Molecular Weight:	93.12
Melting Point:	-70°C
Boiling Point:	129°C
Vapor Pressure:	8 mm Hg at 20°C
Vapor Density:	3.21

2-picoline is freely soluble in water and miscible with alcohol and ether (Windholz, 1976). 2-picoline is used as an organic solvent and intermediate in the dye and resins industries.

II. EXPOSURE

A. Water

Pertinent data could not be located in the available literature.

B. Food

Pertinent data could not be located in the available literature.

C. Inhalation

2-picoline occurs in the working environment of coke oven workers (Naizer and Mashek, 1974) and is present in cigarette smoke (Brennemann et. al., 1979).

D. Dermal

Pertinent data could not be located in the available literature.

III. PHARMACOKINETICS

A. Absorption

In rats, 2-picoline is rapidly absorbed and taken up by the liver, heart, spleen, lungs, brain, and muscles during the first 10 to 20 minutes after oral administration (Kupor, 1972).

B. Distribution

Pertinent data could not be located in the available literature.

C. Metabolism and Excretion

Most of an administered dose in an acute toxicity study was excreted in the urine within 48 hours (Kuper, 1972).

IV EFFECTS

A. Carcinogenicity

Pertinent data could not be found in the available literature.

B. Mutagenicity

Pertinent data could not be found in the available literature.

C. Teratogenicity

The structure and composition of the liver and the structure and growth pattern of the skin were disrupted in the offspring of treated rats who were administered 157 mg per kg body weight of 2-picoline throughout their pregnancy (Nikiforova and Taskaev, 1974).

D. Other Reproductive Effects

Glycolytic processes and protein formation in the liver was disturbed during the pregnancy of rats inhaling 2-picoline at

the maximum permissable concentration for 4 months. The pregnancy complicated toxicosis which without pregnancy was successfully compensated by the liver (Taskaev, 1979).

E. Chronic Toxicity

The following biochemical and physical changes have been observed in rats after the administration of 2-picoline; changes occurred in the liver carbohydrate metabolism (Taskaev, 1979; Kuper and Gruzdeva, 1974) and changes occurred in protein synthesis of the liver noted after chronic oral (Kuper and Gruzdeva, 1974) and inhalation (Taskaev, 1979) exposure. Administration of low doses results in changes in LDH isoenzyme distribution and activity (Gruzdeva, 1976). The major chronic effects of 2-picoline are injury to the liver (Ovchinnikova, 1978; Taskaev, 1979; Ovchinnikova, 1977) and spleen, bone marrow, and lymph nodes (Semchenko, 1973 and 1972).

F. Other Relevant Information

Pertinent data could not be found in the available literature.

V. AQUATIC TOXICITY

A. Acute Toxicity

Pertinent information could not be found in the available literature.

B. Chronic Toxicity, Plant Effects and Residues

Pertinent information could not be found in the available literature.

C. Other Relevant Information

Pertinent information could not be found in the available literature.

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VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The 8-hour, time-weighted average occupational exposure limit for alpha-picoline has been set in Russia at 5 mg/m^3 (Verschueren, 1977). Maximum allowable concentration in Class I waters for the production of drinking waters has been set in the Netherlands at 0.05 mg/l (Verschueren, 1977).

B. Aquatic

Pertinent information could not be found in the available literature.

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No. 149

Polynuclear Aromatic Hydrocarbons (PAH)

Health and Environmental Effects

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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated polynuclear aromatic hydrocarbons and has found sufficient evidence to indicate that this compound is carcinogenic.

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POLYNUCLEAR AROMATIC HYDROCARBONS (PAH)

SUMMARY

The first chemicals ever shown to be involved in the development of cancer belong to the polycyclic aromatic hydrocarbon (PAH) class. Several PAH are well-known as animal carcinogens by all routes of administration. Others are not carcinogenic alone, but in certain cases can enhance or inhibit the tumorigenic response of carcinogenic PAH. Numerous studies of workers exposed to coal gas, coal tars, and coke oven emissions, all of which have large amounts of PAH, have demonstrated a positive association between their exposures and lung cancer development. The carcinogenic risk of ingested PAH in humans, however, has not been extensively studied.

No standard toxicity data for aquatic organisms are available for freshwater or marine life. Limited information concerning toxic responses of freshwater fish reveals that concentrations of 1,000 µg/l for six months produced an 87% mortality in one warm water species.

I. INTRODUCTION

This profile is based primarily upon the Ambient Water Quality Criteria Document for Polynuclear Aromatic Hydrocarbons (U.S. EPA, 1979a) and the Multi-media Health Assessment Document for Polycyclic Organic Matter (U.S. EPA, 1979b).

Polycyclic aromatic hydrocarbons (PAH) are a diverse class of compounds consisting of substituted and unsubstituted polycyclic and heterocyclic aromatic rings. PAH are formed as a result of incomplete combustion of organic material (e.g., fossil fuels, wood, etc.). This leads to formation of C-H free radicals which can polymerize to form various PAH. Among these PAH are compounds such as benzo(a)pyrene (BaP) and benz(a)anthracene (BaA), which are ubiquitous in the environment and well-known for their carcinogenic activity. The presence in ambient air of over one hundred individual PAH has been reported, but quantitative data on only 26 PAH are available thus far.

Most of the PAH are high melting-point, high boiling-point solids that are very insoluble in water. As the ring size increases, the volatility decreases significantly. The PAH are strong absorbers of ultraviolet light, and PAH fluoresce strongly; both of these properties lead to analytical methods for detection of trace quantities. Because of their high melting points and low water solubilities and vapor pressures, most PAH are generally associated with particulate matter. In air, they are adsorbed on small diameter particles that can be easily inhaled. In water, PAH appear to also be primarily associated with particulate matter. Based upon water treatability of PAH, the compounds appear to exist in equal proportions in three forms; bound to large suspended particles; bound to finely dispersed particles, and as the dissolved form (U.S. EPA, 1979a).

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PAH adsorbed to airborne particulate matter appear to be fairly stable in the environment. Nevertheless, some photooxidation occurs with atmospheric PAH since quinone derivatives have been detected in the atmosphere, and their concentrations increase during the summer when the light intensity is greatest.

Considerable study on the microbial and chemical stability and degradation of PAH in the aquatic environment has been conducted. In general, the low molecular weight molecules appear to biodegrade relatively rapidly while PAH containing more than three rings appear to be extremely stable. The first step in the microbial degradation process appears to be the formation of ortho-dihydrodiols which rapidly react to open the ring. PAH also appear to be light sensitive in aquatic systems, but the rate of degradation is difficult to determine experimentally since the vast majority of the compounds are adsorbed to particulate matter. Recent studies have shown that adsorption of many PAH compounds to sediments is a major transport process in aqueous systems. Studies in water treatment of municipal and industrial sewage indicate that about two-thirds of the PAH can be eliminated by sedimentation and biodegradation. If this secondary effluent is subjected to chemical treatment (chlorination or ozonation) the remaining PAH can be degraded.

II. EXPOSURE

A. Water

Based upon work by Basu and Saxena (1978) the average concentrations of BaP, carcinogenic PAH (BaP, benzo(j)fluoranthene, indeno(1,2,3-cd)-pyrene), and total PAH (above 3 compounds plus benzo(g,h,i)perylene, benzo-(b)fluoranthene, and fluoranthene) in U.S. drinking water are 0.55 ng/l, 2.1 ng/l, and 13.5 ng/l, respectively. No drinking water monitoring data on

other PAH compounds are available. The low con- centrations are somewhat a reflection of the extremely low water solu- bilities of PAH compounds. Slightly higher drinking water values have been reported in Europe (e.g. 3-5 ng/l carcinogenic PAH and 40-60 ng/l total PAH), but these differences will have relatively negligible effects on the calculated daily intake values through drinking water compared to other sources (U.S. EPA, 1979a). Assuming that a human consumes approximately 2 liters of water per day, the daily intake of PAH via drinking water would be:

0.55 ng/l x 2 liters/day = 0.0011 µg/day (BaP)
2.1 ng/l x 2 liters/day = 0.0042 µg/day (carcinogenic PAH)
13.5 ng/l x 2 liters/day = 0.0270 µg/day (total PAH)

B. Food

It is difficult to evaluate the human dietary intake of PAH through foods since the amount not only depends on the food habits of the individual and the style of cooking, but it also depends upon the origin of the foods. In order to provide a reasonably accurate estimate of the PAH dietary intake, average concentrations of PAH in representative food items would have to be available. Unfortunately, as of this date, these data have not been generated. However, examination of the available food monitoring data does suggest that a typical range of concentrations for PAH and BaP are 1.0-10.0 ppb and 0.1-1.0 ppb, respectively (U.S. EPA, 1979a). Combining these ranges with average total daily food consumption by man from all types of foods of 1600 g/day, the following estimates of dietary PAH and BaP intake are possible:

0.1 - 1.0 ppb x 1600 g/day = 0.16 - 1.6 µg/day (BaP)
1.0 - 10 ppb x 1600 g/day = 1.6 - 16 µg/day (PAH)

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The U.S. EPA (1979a) has estimated the weighted average bioconcentration factors for the edible portion of all aquatic organisms consumed by Americans. These range from 120 to 24,000, and are based on the octanol-/water partition coefficients for each compound.

C. Ambient Air

It is not possible to determine the average intake of PAH from inhalation of ambient air in the United States because the monitoring data have focused mostly on BaP concentrations. However, by making some assumotions, it is possible to provide estimates that are reasonably close to probable actual values. Using the 1974-1975 Los Angeles monitoring data from Gordon (1976), the relative amounts to carcinogenic PAH and total PAH compared to the average BaP concentration are presented below.

	BaP	Carcinogenic PAH	Total PAH
Ambient conc. ng/m^3	0.5-2.9	2.0	10.9
Inhalation intake, micrograms/day[a]	0.0095-0.0435	0.038	0.207

[a]Assumed average air breathed per day was 19 m^3

III. PHARMACOKINETICS

There are no data available concerning the pharmacokinetics of PAH in humans. Nevertheless, it is possible to make limited assumptions based on the results of animal studies conducted with several PAH, particularly BaP. The metabolism of PAH in human and animal tissues has been especially well-studied, and has contributed significantly to an understanding of the mechanisms of PAH-induced cancer.

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A. Absorption

Regardless of the route of exposure, it can be demonstrated in laboratory animals that PAH are readily absorbed across all epithelia which are in contact with the external environment (Rees, et al. 1971; Kotin, et al. 1969; Vainio, et al. 1976). The fact that PAH are generallly high lipid-soluble neutral molecules greatly facilitates their passage through the predominantly lipid-like cell membranes of animals, including man.

B. Distribution

Upon reaching the bloodstream, PAH are rapidly distributed to most internal body organs (Kotin, et al. 1969; Bock and Dao, 1961; Dao, et al. 1959; Flesher, 1967). Under experimental conditions with laboratory animals, the route of exposure has little apparent influence on the tissue localization of PAH. Extensive localization in the fat and fatty tissues (e.g., breast) is observed (Bock and Dao, 1961; Schlede, et al. 1970 a,b) and suggests that these tissues may act as a chemical trap, creating a situation for sustained release of the unchanged substance. In pregnant rats, it is apparent that BaP and 7,12-dimethylbenz(a)anthracene, but probably not 3-methylcholanthrene, are capable of transplacental passage and localization in the fetus (Shendrikova and Aleksandrov, 1974).

C. Metabolism

PAH are metabolized by the microsomal mixed-function oxidase system, also known as aryl hydrocarbon hydroxylase. This enzyme system is readily inducible and is found in most mammalian tissues, although predominantly in the liver. In conjunction with various P-450 type cytochromes, this enzyme complex is involved in detoxification of many xeno-

biotics, but may also catalyze the formation of reactive epoxide metabolites, themselves leading to carcinogenesis. A second microsomal enzyme, epoxide hydrase, converts epoxide metabolites of PAH to vicinal glycols, a process which may also be of critical importance in the process of carcinogenesis.

Because of the importance of metabolic activation for the expression of carcinogenic effects by PAH, the chemical fate of many representative compounds in mammalian cells has been extensively explored (U.S. EPA, 1979a). By far the most widely studied of the PAH has been BaP, one of the principal carcinogenic products from the combustion of organic material. The metabolites of BaP (and all PAH) can be divided into a water-soluble and an organic solvent-soluble fraction. Components of the latter fraction are primarily ring-hydroxylated products, quinones, and labile epoxide intermediates. For BaP there are at least three dihydrodiols, three quinones, and four phenols which can be detected as positional isomers. The K-region (4,5-) and non-K-region (7,8-; 9,10-) epoxides are precursors of the corresponding vicinal diols, which are formed by the action of the epoxide hydrase enzyme. A subsequent oxidative attack by aryl hydrocarbon hydroxylase may convert the non-K-region diols to vicinal diol epoxides, one of which (7,8-diol-9,10-epoxide) is an ultimate carcinogenic form of BaP.

In the water-soluble fraction containing BaP metabolites are mainly conjugates of hydroxylated products with glutathione, glucuronic acid, and sulfate. This group of metabolies is tentatively regarded to be composed of non-toxic excretion products.

The general scheme of metabolism for unsubstituted PAH closely parallels that for BaP, although several other major environmental PAH have not been studied. It is also evident that K-region derivatives of PAH may be preferred targets for conjugation and excretion, whereas non-K-region epoxides undergo further reductions and oxidative attack to form toxicologically important molecules. For PAH bearing alkyl substituents (e.g., DMBA, MCA), the primary metabolites formed are hydroxymethyl derivatives. Nevertheless, epoxidation reactions at K-region and non-K-region aromatic double bonds occur which are catalyzed by aryl hydrocarbon hydroxylase. Removal of activated intermediates occurs by conjugation with glutathione or glucuronic acid, or by further metabolism to tetrahydrotetrols.

D. Excretion

Over forty years ago, researchers recognized that various PAH were excreted primarily through the hepatobiliary system and the feces (Peacock, 1936; Chalmers and Kirby, 1940). However, the rate of disappearance of various PAH from the body, and the principal routes of excretion are influenced both by structure of the parent compound and the route of administration (Heidelberger and Weiss, 1959; Aitio, 1974a,b). Moreover, the rate of disappearance of a PAH (i.e., benzo(a)pyrene) from body tissues can be stimulated markedly by prior treatment with inducers of microsomal enzymes (e.g., benzo(a)pyrene, 7,12-dimethylbenz(a)anthracene, 3-methylcholanthrene, chrysene) (Schlede, et al. 1970a,b). Likewise, it has been shown that inhibitors of microsomal enzyme activity, such as parathion and paraoxon, can decrease the rate of BaP metabolism in certain animal tissues (Weber, et al. 1976). From the available data concerning excretion of PAH in animals, it is apparent extensive bioaccumulation is not likely to occur.

IV. EFFECTS

A. Carcinogenicity

PAH were the first compounds ever shown to be associated with carcinogenesis. As of this date, carcinogenic PAH are still distinguished by several unique features: (1) several of the PAH are among the most potent carcinogens known to exist, producing tumors by single exposures to microgram quantities; (2) they act both at the site of application and at organs distant to the site of absorption; and (3) their effects have been demonstrated in nearly every tissue and species tested, regardless of the route of administration (U.S. EPA, 1979a). Among the more common PAH, at least one, BaP, is ubiquitous in the environment. In animals, PAH produce tumors which resemble human carcinomas. The demonstration that organic extracts of particulate air pollutants are carcinogenic to animals has raised concern over the involvement of PAH in human cancer formation (Hoffmann and Wynder, 1976).

Oral administration of PAH to rodents can result in tumors of the fore-stomach, mammary gland, ovary, lung, liver, and lymphoid and hematopoietic tissues (U.S. EPA, 1979a). Exposure to very small doses of PAH by inhalation or intratracheal instillation can also be an effective means of producing tumors of the respiratory tract. However, for both oral and intratracheal routes of administration, BaP is less effective than other PAH (e.g., DMBA, MCA) in producing carcinomas. However, BaP has a remarkable potency for the induction of skin tumors in mice that cannot be matched by any other environmental PAH. Therefore, caution must be exercised in considering the carcinogenicity of PAH as a class, or in using BaP as a representative example in evaluating the carcinogenic risk of PAH.

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The presence of PAH in the air, or as components of soot, tars, and oils, have long been associated with an excess incidence of cancer in human populations (U.S. EPA, 1979a,b). However, it has never been possible to study a population having exposure to PAH in the absence of other potential carcinogens, cocarcinogens, tumor initiators, or tumor promoters.

Convincing evidence from air pollution studies indicates an excess of lung cancer mortality among workers exposed to large amounts of PAH-containing materials such as coal gas, tars, soot, and coke-oven emissions (Kennaway, 1925; Kennaway and Kennaway, 1936, 1947; Henry, et al. 1931; Kuroda, 1937; Reid and Buck, 1956; Doll, 1952; Doll, et al. 1965, 1972; Redmond, et al. 1972, 1976; Mazumdar, et al. 1975; Hammond, et al. 1976; Kawai, et al. 1967). However, no definite proof exists that the PAH present in these materials are responsible for the cancers observed. Nevertheless, our understanding of the characteristics of PAH-induced tumors in animals, and their close resemblance to human carcinomas of the same target organs, suggests PAH pose a carcinogenic threat to man, regardless of the route of exposure.

B. Mutagenicity

The demonstration of mutagenicity in bacterial and mammalian cells by exposure to PAH is generally equated with the capability to induce tumor formation. This assumption is based on the participation of a common electrophilic metabolite in producing the carcinogenic/mutagenic event, and the common target site in the cell (i.e., DNA or other components of the genome) for the effect to be produced.

In recent years, considerable research effort has been directed at determining the mutagenicity of various PAH derivatives as a means of identifying structural features associated with the biological effect produced.

Working with bacterial mutants which can be reverted to histidine independence by a chemically-induced mutation, epoxides of carcinogenic PAH were shown to possess significant mutagenicity (U.S. EPA, 1979a). Further work with cultured mammalian cells established that carcinogenic PAH can produce forward mutations when a drug metabolizing enzyme system is available (Huberman and Sachs, 1974, 1976).

Numerous attempts have been made to correlate exposure to PAH with the induction of chromosomal aberrations. Although variations in chromosome number and structure accompany PAH-induced tumors in rodents, it is not clear whether these changes are consistently observable (U.S. EPA, 1979a,b). No evidence in the published literature has been found to indicate that PAH may produce somatic mutations in the absence of neoplastic transformation.

C. Teratogenicity

PAH are not generally regarded to have significant teratogenic activity. BaP showed no effect on the developing embryo in several mammalian and non-mammalian species (Rigdon and Rennels, 1964; Rigdon and Neal, 1965). In contrast, DMBA and its hydroxymethyl derivatives apparently are teratogenic in the rat, but only at high doses (Currie, et al. 1970; Bird, et al. 1970).

D. Other Reproductive Effects

Little additional information is presently available to indicate whether PAH present a significant hazard to reproductive success. Furthermore, effects on the fetus which may be due to maternal toxicity or experimental conditions (e.g., injection vehicle, stress) have not been adequately dissociated from true embryotoxicity or teratogenesis.

E. Chronic Toxicity

Little attention has been paid to the non-carcinogenic effects of exposure to PAH. Nevertheless, it is known that tissues of the rapidly proliferating type (e.g., intestinal epithelium, bone marrow, lymphoid organs, testis) seem to be the preferred targets for PAH-induced cytotoxicity (U.S. EPA, 1979). This action is probably due to a specific attack on DNA of cells in the S phase of the mitotic cycle (Philips, et al. 1972).

Acute and chronic exposure to various carcinogenic PAH has resulted in selective destruction of hematopoietic and lymphoid elements, ovotoxicity and anti-spermatogenic effects, adrenal necrosis, and changes in the intestinal and respiratory epithelia (U.S. EPA, 1979a). For the most part, however, tissue damage occurs at dose levels that would also be expected to induce carcinomas, and thus the threat of malignancy predominates in evaluating PAH toxicity. For the non-carcinogenic PAH, there is a shortage of available data concerning their involvement in toxic responses.

V. AQUATIC TOXICITY

A. Acute Toxicity

Standard toxicity determinations for freshwater or marine organisms have not been conducted for any PAH. The marine worm, Neanther arenaceodenta, was exposed to crude oil extracts, and LC_{50} values for various PAH ranged from 300 to 1,000 µg/l (Neff, et al. 1976a,b). A 90 percent lethality, determined from photodynamic response, was obtained for the protozoa, Paramecium caudatum at an for anthracene concentration of 0-1 µg/l in one-hour exposures (Epstein, 1963). Bluegill sunfish (Lepomis macrochirus) displayed an 87% mortality at concentration of 1,000 µg/l benzo-a-anthracene.

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B. Chronic

Standard toxicity studies using either freshwater or marine organisms have not been conducted on any PAH. A six-month study of benzo-(a)pyrene on the bluegill sunfish (Lepomis macrochirus) produced 87 percent mortality at a concentration of 1,000 ug/l (Brown, et al. 1975).

C. Plants

Studies of the effects of PAH on freshwater or marine plants could not be located in the available literature.

D. Residues

In short-term modeling of freshwater ecosystem studies, three-day bioconcentration factors for benzo(a)pyrene of 930, 5,258, 11,536, 82,231, and 134,248 were obtained for the mosquito-fish (Gambusia affinis), the algae Oedogonium cardiacum, the mosquito Culex pipiens quinquefasciatus, the snail Physa sp., and cladoceran Daphnia pulex, respectively (Lu, et al. 1977). For anthracene, a 1-hour bioconcentration factor of 200 was obtained for Daphnia magna (Herbes, 1976). For marine molluscs, bioconcentration factor values ranged from 8.2 for the clam (Rangia cuneata) (Neff, et al. 1976a) to 242 for the eastern oyster (Crassostrea virginica) (Couch, et al., in press).

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health and aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have not gone through the process of public review; therefore, there is a possibility that these criteria may be changed.

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A. Human

To date, one recommended standard for PAH as a class has been developed. The World Health Organization (1970) recommends a concentration of PAH in water not to exceed 0.2 µg/l. This recommended standard is based on the composite analysis of six PAH in drinking water: (1) fluoranthene, (2) benzo(a)pyrene, (3) benzo(g,h,i)perylene, (4) benzo(b)-fluoranthene, (5) benzo(k)fluoranthene, and (6) indeno(1,2,3-cd)pyrene.

In the occupational environment, a Federal standard has been promulgated for coke oven emissions, based primarily on the presumed effects of the carcinogenic PAH contained in the mixture as measured by the benzene soluble fraction of total particulate matter. Similarly, the American Conference of Governmental Industrial Hygiensists recommends a workplace exposure limit for coal tar pitch volatiles, based on the benzene-soluble fraction containing carcinogenic PAH. The National Institute for Occupational Safety and Health has also recommended a workplace criterion for coal tar products (coal tar, creosote, and coal tar pitch), based on measurements of the cyclohexane extractable fraction. These criteria are summarized below:

Substance	Exposure Limit	Agency
Coke Oven Emissions	0.150 mg/m^3, 8-hr. time-weighted average	U.S. Occupational Safety and Health Administration
Coal Tar Products	0.1 mg/m^3, 10-hr. time-weighted average	U.S. National Institute for Occupational Safety and Health
Coal Tar Pitch Volatiles	0.2 mg/m^3, (benzene soluble fraction) 8-hr. time-weighted average	American Conference of Governmental Industrial Hygienists

Based on animal bioassay data, and using the "one-hit" model, the U.S. EPA (1979a) has set draft ambient water quality criteria for BaP and dibenz(a,h)anthracene (DBA) which will result in specified risk levels of human cancer as shown in the table below.

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BaP

Exposure Assumptions (per day)	Risk Levels and Corresponding Draft Criteria ng/l			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish.	0	0.275	2.75	27.5
Consumption of fish and shellfish only.	0	1.25	12.5	125

DBA

Exposure Assumptions (per day)	Risk Levels and Corresponding Draft Criteria ng/l			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish.	0	0.43	4.3	43
Consumption of fish and shellfish only.		1.96	19.6	196

B. Aquatic

Criteria have not been proposed for the protection of aquatic organisms (U.S. EPA, 1979a).

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Pyridine

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DISCLAIMER

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PYRIDINE

Summary

Pyridine has not shown carcinogenic effects following repeated subcutaneous administration to rats; the compound did not show mutagenic activity in the Ames Salmonella assay.

A single study has indicated that pyridine produced developmental abnormalities when administered to chicken embryos.

Chronic exposure to pyridine produces CNS disturbances and may produce adverse hepatic and renal effects.

Pyridine has been shown to be toxic to freshwater fish at concentrations ranging from 100,000 to 1,580,000 µg/l. For freshwater invertebrates, toxic concentrations of pyridine range from 575,000 to 2,470,000 µg/l.

150-3

I. INTRODUCTION

Pyridine (CAS number 110-86-1) is a colorless liquid possessing a sharp, penetrating odor. It has the following physical properties:

Formula:	C_5H_5N
Molecular Weight:	79.1
Melting Point:	-42°C
Boiling Point:	115.3°C
Density:	0.982
Vapor Pressure:	10 mm Hg at 13.2°C (Sax, 1975)
Solubility:	miscible with water, alcohol, ether, and other organic solvents (Windholz, 1976)

Pyridine is a weak base and forms salts with strong acids. It is used as a solvent for anhydrous mineral salts, in various organic synthetic preparations, and in analytical chemistry (Windholz, 1976). The estimated annual production of pyridine is in excess of 60 million pounds (Federal Register 43:16688, April 19, 1978).

II. EXPOSURE

A. Water

Pertinent data could not be located in the available literature.

B. Food

Reported levels of pyridine in foods include: from 0.02 to 0.12 ppm, ice cream; 0.4 ppm, baked goods; 1.0 ppm, non-alcoholic beverages; 0.4 ppm, candy. Pyridine has also been found to occur naturally in coffee and tobacco (Furia, 1975).

C. Inhalation

Pyridine may be produced and released during the combustion of coke and as a combustion product in cigarette smoke (Graedel, 1978).

The major release of pyridine is from emissions from manufacturing and chemical processes. Based on total annual production, the U.S. EPA (1976) has estimated a significant potential emission of pyridine during manufacture.

D. Dermal

Pertinent data could not be located in the available literature.

III. PHARMACOKINETICS

A. Absorption

Absorption of pyridine occurs through the respiratory and gastrointestinal tracts, but probably not through the skin (Gosselin, et al. 1976).

B. Distribution

Pertinent data could not be located in the available literature.

C. Metabolism and Excretion

Pyridine may be partly excreted unchanged or may be methylated at the N-position (Patty, 1963) and excreted as N-methyl pyridinium hydroxide, its chief metabolite (Browning, 1965). Methylation occurs in mice but not in rats, and it may occur to some extent in man The fate of the majority of absorbed pyridine is not known (Browning, 1965).

IV. EFFECTS

A. Carcinogenicity

Subcutaneous injection of pyridine at levels of 3 to 100 mg/kg twice weekly for a year did not produce tumors in rats (Mason, et al. 1971).

B. Mutagenicity

Pyridine did not show mutagenic effects with activation in the Ames Salmonella assay (Commoner, 1976).

C. Teratogenicity

Pyridine caused chick embryo abnormalities in one limited study (Federal Register 43:16688, April 19, 1978).

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D. Other Reproductive Effects

Pertinent data could not be located in the available literature.

E. Chronic Toxicity

Prolonged daily exposure to pyridine at levels from 6 to 12 ppm causes mild central nervous system (CNS) disturbances in workers, while exposure from 15 to 330 ppm causes insomnia, nervousness, and low-back or abdominal pain accompanied by frequent urination (Gosselin, et al. 1976).

In animals, the major effects of repeated feeding of pyridine are hepatic and renal injury (Patty, 1963). Chronic exposure to 10 or 50 ppm pyridine vapors causes increased liver/body weight ratios in rats (ILO, 1971).

F. Other Relevant Information

Symptoms in humans associated with inhalation or ingestion of pyridine are CNS depression, and liver and kidney damage (Federal Register 4:16688, April 19, 1978; Gosselin, et al. 1976; Sax, 1975; ILO, 1971). Vapors are also irritating to eyes, skin, and nasal membranes (ACGIH, 1977; Sax, 1975). Skin eruptions induced by pyridine may be provoked by exposure to light (Arena, 1974). Ingestion of pyridine causes CNS depression, heart and gastrointestinal distress, fever, and, at high doses, death; and may stimulate bone marrow production of platelets in low doses (ACGIH, 1977; Gosselin, et al. 1976). Death may be due to either hepatic or renal damage, or from pulmonary injury (Gosselin, et al. 1976; ACGIH, 1977).

Exposure to vapors of pyridine from 1,250 to 10,000 ppm for 1 to 7 hours did not cause mortality in rats, but a 0.1 percent diet of pyridine induced rapid weight loss and death in two weeks (ILO, 1971).

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V. AQUATIC TOXICITY

A. Acute Toxicity

McKee and Wolf (1963) have reviewed the effects of pyridine on several aquatic organisms. The freshwater minnow, bleak (Alburnus lucidus), was the most sensitive species tested with threshold toxicities ranging from 100,000 to 160,000 µg/l. Tests with the freshwater mosquitofish (Gambusia affinis) revealed a 96-hour LC_{50} value of 1,300,000 µg of pyridine per liter of turbid water. Orange-spotted sunfish (Lepomis humilis) were killed in one hour from exposure to pyridine at concentrations ranging from 1,480,000 to 1,580,000 µg/l, while goldfish (Carassius auratus) were killed after 10 to 30 hours' exposure to pyridine. Verschueren (1979) has reported a 24-hour LC_{50} value of 1,350,000 µg/l for mosquitofish exposed to pyridine.

Dowden and Bennett (1965) demonstrated a 48-hour LC_{50} value of 2,114,000 µg/l for Daphnia magna exposed to pyridine. McKee and Wolf (1963) reported a threshold effect of 40,000 µg/l for Daphnia sp. Canton and Adema (1978) determined 48-hour LC_{50} values ranging from 1,130,000 to 1,755,000 µg/l for Daphnia magna, and 48-hour LC_{50} values of 575,000 and 2,470,000 µg/l for Daphnia pulex and Daphnia cucullata, respectively.

B. Chronic Toxicity, Plant Effects and Residues

Pertinent data could not be located in the available literature.

C. Other Relevant Information

Thomas (1973) reports that pyridine exposure levels of 5,000 µg/l impart an off-flavor to fish flesh.

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VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The 8-hour, time-weighted-average occupational exposure limit for pyridine recommended by the American Conference of Governmental Industrial Hygienists is 5 ppm (ACGIH, 1977).

B. Aquatic

Based on 96-hour LC_{50} data, Hahn and Jensen (1974) have assigned pyridine an aquatic toxicity rating of from 100,000 to 1,000,000 µg/l.

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No. 151

Quinones

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

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QUINONE

Summary

Quinone has been reported to produce neoplasms, but insufficient data are available to assess its carcenogenic potential. Quinone was not mutagenic to Orosophila melanogaster, human leukocytes, nor Neurospora.

Quinone is very toxic to fish and plants. Exposure to humans causes conjunctival irritation and, in some cases, corneal edema, ulceration, and scarring; transient eye irritation was noted above 0.1 ppm. Quinone is highly toxic to mammals via the oral and inhalation route.

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I. INTRODUCTION

Quinone (p-Benzoquinone; Cas No. 106-51-4) is a yellow, crystalline solid with chlorine-like irritating odor. It has the following physical properties:

Formula:	$C_6H_4O_2$
Physical State:	large, yellow, monoclinic prisms
Molecular Weight:	108.09
Specific Gravity:	1.318 (20°C)
Melting Point:	112.9°C
Boiling Point:	sublimes
Vapor Pressure:	considerable; sublimes readily upon gentle heating (Patty,1967)

Quinone is soluble in alcohol, ether, and alkali; and slightly soluble in hot water. Quinone can be prepared by oxidation starting with aniline or by the reduction of hydroquinone with bromic acid. The compound has found wide application in the dye, textile, chemical, tanning, photography, and cosmetic industries primarily because of its ability to transform certin nitrogen-containing compounds into a variety of colored substances (Patty, 1967).

II. EXPOSURE

A. Water

Pertinent data could not be located in the availabe literature.

B. Food

Pertinent data could not be located in the available literature.

C. Inhalation

Because of its ability to sublime, quinone becomes an air contaminant problem at the production site.

D. Dermal

Pertinent data could not be located in the available literature.

III. PHARMACOKINETICS

A. Absorption

Quinone is readily absorbed from the gastroenteric tract and subcutaneous tissues (Patty, 1967). Sax, 1979, reports quinine as capable of causing death or permanent injury due to the exposures of normal use via absorption through oral and inhalation routes. Quinone affects the eyes (Procter, 1978).

B. Distribution

Pertinent data could not be located in the available literature.

C. Mebalolism and Excretion

Quinone is partially excreted unchanged; but the bulk is eliminated in conjugation with hexuronic, sulfuric, and other acids (Patty, 1967).

IV. EFFECTS

A. Carcinogenicity

Quinone has been reported to produce neoplasms but upon review by the International Agency for Research on Cancer, it was determined that there was insufficient data to conclude that it was a carcinogen (IARC, 1977)

B. Mutagenicity

Quinone did not produce mutagenic effects in studies with

Drosophila melanogaster and human leukocytes (Lueers and Obe, 1972). Another study reported quinone as nonmutagenic to Neurospora (Reissig, 1963).

C. Teratogenicity

Pertinent data could not be located in the available literature.

D. Other Reproductive Effects

Pertinent data could not be located in the available literature.

E. Chronic Toxicity

Quinone has been reported to oxidize with the lens protein SH groups in rabbits (Ikemota and Augusteyn, 1976). Chronic exposure causes the gradual development of changes characterized as follows: brownish discoloration of the conjunctiva and cornea confined to the intrapalpebral fissure; small opacities of the cornea; and structural corneal changes which result in loss of visual acuity (Sterner, et al., 1947; Anderson and Oglesby, 1958).

F. Other Relevant Information

Acute exposure causes conjunctival irritation and, in some cases, corneal edema, ulceration, and scarring; transient eye irritation may be noted above 0.1 ppm and becomes marked at 1 to 2 ppm (AIHA, 1963). Ulceration of the cornea has resulted from one brief exposure to a high concentration of the vapor of quinone, as well as from repeated exposures to moderately high concentrations (Patty, 1967). Absorption of large doses of quinone from the gastroenteric tract or from subcutaneous tissues of animals induces chronic convulsions, respiratory difficulties, drop in blood pressure, and death by paralysis of the medullary centers (Patty, 1967).

Oral rat LD50s have been reported for quinone ranging from 130 to 296 mg per kg body weight (Verschueren, 1977). Inhalation of quinone at concentrations ranging from 230 to 270 mg per cu.m. for 2 hrs was lethal to 100 percent of the test population of rats.

IV. AQUATIC TOXICITY

A. Acute Toxicity

Quinone has been reported to be toxic to invertebrate Daphnia at 0.4 ppm (Verschueren, 1977). Also, quinone has an LD50 for perch ranging from 5 to 10 mg/l (Verschueren, 1977).

B. Chronic Toxicity, Plant Effects, and Residues

Quinone inhibits photosynthesis in the fresh water algae S. capricornutum (Gidding, 1979), decreases chlorophyll flourescence and cyclosis (protoplasmic streaming) of Nitella cells (Apartsin, et al, 1979; Stom, 1977; Stom and Kuzevania, 1976; Stom and Rogozina, 1976), and inhibits carbon metabolism in Chlorella pyrenoidosa (Printavu, 1975).

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The 8-hour, time-weighted average occupational exposure limit for quinone has been set in the United States at a concentration of 0.1 ppm and in the U.S.S.R. at a concentration of 0.01 ppm (Verschueren, 1977).

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No. 152

Resorcinol

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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RESORCINOL

Summary

Resorcinol, 1,3-dihydroxybenzene, is a phenolic compound. Resorcinol is weakly antiseptic and resorcinol compounds are used in pharmaceuticals and hair dyes for human use. Major industrial uses are as adhesives in rubber products and tires, wood adhesive resins, and as ultraviolet absorbers in polyolefin plastics. Resorcinol is also a byproduct of coal conversion and is a component of cigarette smoke. Thus, substantial opportunity exists for human exposure.

Many phenolic compounds, including resorcinol, are strong mitotic spindle poisons in plants. This evidence of mutagenic activity and the strong oncogenic activity in plants have not been adequately tested in animals to provide an understanding of the processes. In animals the only cocarcinogenic activity (in cigarette smoke condensate) demonstrated has been as a protective agent against benzo(a)pyrene carcinogenicity.

Resorcinol has been demonstrated to result in chronic toxicity: reducing growth rate in an insect species and causing chronic health complaints from workers in a tire manufacturing plant.

Acute toxicity through oral, eye, skin penetration, and skin irritation has been demonstrated by all tests. Values vary in the literature and are inadequate to draw a quantitative conclusion. Resorcinol has also been shown to be acutely toxic to both freshwater and marine aquatic organisms in 96-hour LC_{50} tests.

No standards or guidelines exist for resorcinol. ACGIH's Committee on Threshold Limits has proposed a TLV of 5 ppm but has not finalized that recommendation. Industry has suggested this value is lower than is required for safety, citing existing workplace levels of 9.6 ppm without worker complaint or evidence of acute or chronic toxicity.

I. INTRODUCTION

Resorcinol is a phenolic compound (molecular weight, 110.1; boiling point, 276^{0}C; melting point, 110.0^{0}C). Synonyms are m-dihydroxybenzene, 1,3-benzenediol, 3-hydroxyphenol, and resorcin. Resorcinol occurs as white or nearly white needle-shaped crystals or powder. It has a faint, characteristic odor and a sweetish taste with a bitter aftertaste. One gram is soluble in 1 ml of water and in 0.1 ml of alcohol.

Resorcinol is a weak antiseptic and is used in antiseptics, keratolytic disease treatments and fungicides (Wilson, et al. 1977). Major uses of resorcinol are: in tires and other rubber products; wood adhesive resins; as an ultraviolet absorber in polyolefin plastics; as an intermediate in dye manufacture (especially hair dyes); and in the production of synthetic tanning agents, explosives, and specialty adhesives. The tire and rubber industries accounted for 43 percent of the use of resorcinol in 1974, primarily as adhesives in fabricating belting, rubberized hose, and rubberized textile sheets (Stanford Research Institute, 1975).

Resorcinol is expected to be a component of various waste streams from coal conversion facilities. The potential for removal through existing waste treatment processes is currently under assessment (Herbes and Beauchamp, 1977).

II. EXPOSURE

Resorcinol is used in substantial quantities in industry and frequently in small quantities in the home. Although the potential for human exposure exists, very little exposure information is available. The Koppers Company, Inc., Monroeville, Pennsylvania, is the major supplier of resorcinol in the United States. They report substantial testing of the plant environment indicating resorcinol concentration up to 9.6 ppm in ambient air (Flickinger, 1976).

Resorcinol is currently sold and transported as a solid, although the Koppers Company reports increasing inquiries regarding bulk shipments of molten resorcinol. They indicate that this would increase the opportunity for industrial and public exposure to the compound (Flickinger, 1976).

In an epidemiological study of rubber workers at a hexamethylenetetramine-resorcinol (HR) resin system tire manufacturing plant, all environmental samples in the study were less than 1 mg/m^3 (Gamble, et al. 1976).

Resorcinol has been shown to be present in cigarette smoke and is a component of the weakly acidic fraction of cigarette smoke condensate which has been shown to have tumor-promoting capability (Schlotzhauer, et al. 1978).

III. PHARMACOKINETICS

Despite the presence of resorcinol and resorcinol compounds in numerous pharmaceutical preparations, no specific information on the metabolism, distribution, absorption, or excretion of resorcinol was found in the available literature.

IV. EFFECTS

A. Carcinogenicity

The available data dealing with the potential carcinogenicity of resorcinol are at this time inadequate to formulate a clear understanding of resorcinol's oncogenic potential. In a study of commonly used cutaneous agents, Stenbäck (1977) showed no tumor induction in rabbits and mice from topically applied resorcinol. Resorcinol was selected because of its presence in hair dyes.

Van Duuren and Goldschmidt (1976), in a study of 21 tobacco smoke components, found that resorcinol reduced the carcinogenic potential of benzo(a)pyrene (BaP) in dermal application to mice. Thus, fewer tumors were

induced by BaP in the presence of resorcinol, indicating possible inhibition of carcinogenic activity.

Substantial evidence appears to exist for the oncogenic activity of resorcinol in plants. Anderson (1973) reports that the "strong carcinogenicity" of resorcinol tested in Nicotiana hybrids suggests that "an oncogenic reactivity of phenols is common to plant and animal tissues but with differences in strength of reaction to a derivative in a given system".

B. Mutagenicity

Dean (1978) reports that most phenolic compounds including resorcinol are mitotic spindle poisons in plant tissues. He further reports that considering the severity of effects on plant chromosomes that it is surprising that in vivo plant and animal tests have not been done to determine their clastogenic properties.

By micronucleus test, Hossack and Richardson (1977) were unable to find evidence of mutagenicity in resorcinol or a number of other hair dye constituents tested.

The Ames assay for resorcinol was negative in a test of commonly used cutaneous agents (Stenbäck, 1977).

C. Teratogenicity and Other Reproductive Effects

Pertinent data could not be located in the available literature.

D. Chronic Toxicity

In a study of chronic toxicity effects on the black cutworm, Agrotis epsilon, Reese and Beck (1976) found no significant correlation between resorcinol concentration and pupation or survival but found correlation with body weight at various stages of development. They report that resorcinol is the only compound among those tested which had "no adverse effect on any of the nutritional indices and yet reduced growth. It is also the only com-

pound which inhibited growth but did not inhibit pupation." They hypothesized that resorcinol may act through a temporary inhibition of ingestion but that the insects continued to eat regularly, allowing pupation on a normal schedule (Reese and Beck, 1976).

In the epidemiological study of the HR resin system tire manufacturing plant, Gamble, et al. (1976) reported that HR exposed workers consistently showed an excess of respiratory symptoms and that there was a consistent association of alcohol consumption with increased incidence of symptoms. The reported symptoms included rash, itch, difficult breathing at work, cough, chest tightness, burning eyes, running nose, and burning sensation in the heart region.

E. Acute Toxicity

With one exception, all acute toxicity data in the readily available literature are supplied by Flickinger (1976) for the Koppers Company, the primary manufacturer and supplier of resorcinol in the United States. Lloyd, et al. (1977) independently reported the LD_{50} for acute oral toxicity to be 370 mg/kg for resorcinol.

In a review of the industrial toxicology of the benzenediols, Flickinger (1976) reports various acute toxicity data for resorcinol. A summary of relevant results follows:

An acute oral LD_{50} for resorcinol was reported by Flickinger (1976) as 0.98 gm/kg in the rat. Rats dying during the period showed hyperemia and distension of the stomach and intestines. Surviving rats showed normal weight and no gross lesions at necropsy.

The LD_{50} for dermal application in the rat was 3.36 gm/kg. At higher levels, resorcinol produced skin necrosis. At 1.0 gm/kg levels,

moderate to severe irritation was followed in 24 hours by slight hyperkeratosis. Surviving rats showed reduced weight but no internal gross lesions upon necropsy.

Flickinger (1976) reported that resorcinol is a severe eye irritant (0.1 gm in eye of male, albino rabbits). No recovery was seen in the 14-day follow-up period with all exposed individuals exhibiting keratoconus and pannus formation.

Resorcinol is a primary skin irritant. Contact with 0.5 gm of resorcinol on intact and abraided skin produced moderate irritation on intact skin and varying reactions including necrosis on abraided skin.

Inhalation of up to 2,800 mg/m^3 of resorcinol aerosol for 8 hours resulted in no observable toxic effects to the rats (Flickinger, 1976).

V. AQUATIC TOXICITY

The possibility that resorcinol may be present in some quantity in coal conversion process effluents requires further investigation as to the feasibility of control technology. Herbes and Beauchamp (1977) compared toxic interactions of two coal conversion effluents, resorcinol and 6-methylquinaline. With Daphnia magna as a test species, they found mixtures of the two compounds to be less toxic than either pure compound tested alone. They report a 48-hour LC_{50} for resorcinol alone to be 1.28 mg/l.

Curtis, et al. (1979) reported the acute toxicity of resorcinol to freshwater and saltwater organisms. In freshwater, the LC_{50} values for fathead minnow are as follows: 24 hours, 88.6 mg/l; 48 hours, 72.6 mg/l; and 96 hours, 53.4 mg/l. In saltwater, the LC_{50} values for Palaemonetes pugio or Penaeus setiferus are: 24 hours, 169.5 mg/l; 48 hours, 78.0 mg/l; and 96 hours, 42.4 mg/l. Thus, resorcinol was found to be toxic to aquatic life in both freshwater and saltwater.

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VI. EXISTING GUIDELINES AND STANDARDS

There are no OSHA regulations, NIOSH recommendations, or other guidelines concerning resorcinol. In 1974, ACGIH's Committee on Threshold Limits proposed a TLV for resorcinol of 5 ppm. Flickinger (1976) reports of current industrial 8-hour workday exposures at 9.6 ppm "without signs of intoxication or skin or respiratory irritation" and recommends TLV industrial exposures of "at least 10 ppm, perhaps even 20 ppm or higher". ACGIH has not issued a formal TLV for resorcinol.

Information regarding existing guidelines and standards to protect aquatic life from the effects of resorcinol was not found in the available literature.

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No. 153

Selenium

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

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153-2

SELENIUM

SUMMARY

Human daily intake of selenium has been estimated at 50 to 150 µg/day. While selenium is an essential nutrient for humans and other species, it is toxic in excessive amounts. Selenium poisoning produces symptoms in man similar to those produced by arsenic. Although it has been shown to produce tumors in animals, the Food and Drug Administration, the International Agency for Research on Cancer and the National Academy of Science have concluded that the available animal data are insufficient to allow an evaluation of the carcinogenicity of selenium compounds.

The data base for selenium for aquatic life is quite limited. No chronic data are available for marine fish. Selenium does not bioconcentrate to a great extent in freshwater species, indicating that tissue residues should not be a hazard to freshwater organisms. This information is not available for marine organisms.

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153-3

SELENIUM

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Selenium (U.S. EPA, 1979).

Selenium (Se; atomic weight 78.96) is a naturally occurring element which reacts with metals to form ionic selenides with a valence of minus 2, and with most other chemials to form covalent compounds. It may assume any of several valence states ranging from minus 2 to plus 6. Selenium is used in photocopying, the manufacture of glass, electronic devices, pigments, dyes and insecticides (Dept. Interior, 1974). It is also used in veterinary medicine (U.S. EPA, 1979) and in antidandruff shampoos (Cummings and Kimura, 1971). The major source of selenium in the environment is the weathering of rocks and soils (Rosenfeld and Beath, 1964) but human activities contribute about 3,500 metric tons per year (U.S. EPA, 1975a). Selenium is an essential nutrient for humans and other species (Schroeder, 1970).

II. EXPOSURE

Selenium is not present in measurable quantities in most U.S. drinking water supplies. Of 3,676 residences located in 35 geographically dispersed areas, only 9.96 percent of the samples had selenium levels above the detection limits of 1 µg/l (Craun, et al. 1977). However, in seleniferous areas of South Dakota, levels of 50 to 330 µg/l were measured in drinking waters (Smith and Westfall, 1937). Sewage plant effluents may contribute to the selenium content of water; as much as 280 µg/l have been reported in raw sewage, 45 µg/l in primary effluent, and 50 µg/l

in secondary effluent (Baird, et al. 1972). Selenium concentrations in plants depend largely on the concentration in the soil where the plants are grown. High selenium concentration in vegetation is transmitted to other food sources, e.g., meats and eggs. The EPA (1979) has estimated the weighted average bioconcentration factor for selenium to be 18 for consumed fish and shellfish. Zoller and Reamer (1976) reported that most urban regions have concentrations of particulate selenium ranging from 0.1 to 10 ng/m^3.

III. PHARMACOKINETICS

A. Absorption

Selenium appears to be effectively absorbed by the gastrointestinal tract. Thomson and Stewart (1974) reported absorptions of 70, 64, and 44 percent for sodium selenite in three young women. Data from rats are similar with absorptions ranging from 81 to 97 percent for a number of organic selenium compounds and sodium selenite (Thomson and Stewart, 1973; Thomson, et al. 1975). The literature contains no information on absorption by inhalation or dermal exposures (National Research Council, 1976).

B. Distribution

The primary disposition sites for selenium in the body are the liver, kidney, spleen, and middle and lower sections of the small intestine (U.S. EPA, 1979). Based on the work of Kincaid, et al. (1977) it is apparent that tissue concentration levels of selenium can be affected both by dose and normal dietary intake, although the primary deposition sites remain the same.

C. Metabolism

Selenium is an essential element and at nutritional levels it is incorporated into specific functional proteins; at higher concentrations, it is substituted for sulfur in sulfur-containing compounds. Selenium analogs are often less stable than sulfur compounds, and this lability may be the basis of toxicity (Stadtman, 1974). Selenite and selenate are methylated by mammalian tissues in an apparent detoxification process. Mouse liver, lung and kidney (Ganther, 1966) are active in methylation, but muscle, spleen, and heart have little activity.

D. Excretion

Thomson and Stewart (1974) studied selenium excretion by feeding three women selenite. It was apparent that the primary routes of excretion were in the feces and urine, with little loss through the skin or lungs.

IV. EFFECTS

A. Carcinogenicity

Only six studies have been performed to specifically investigate whether selenium is carcinogenic. From these studies there is no conclusive evidence that selenium has induced tumors in the test animals. The Food and Drug Administration has declared that selenium poses no carcinogenic risk (Food and Drug Administration, 1973).

B. Mutagenicity

Selenium has been shown to affect the genetic process in barley (Walker and Ting, 1967) and in Drosophila melanogaster (Ting and Walker, 1969; Walker and Bradley, 1969). However, these

and other genotoxic effects are not true mutagenic effects. There is no study in which a true mutagenic activity for selenium has been demonstrated.

C. Teratogenicity

The consumption of seleniferous diets interfered with the normal development of the embryo in many mammalian species, including rats, pigs, sheep and cattle (U.S. EPA, 1979). Robertson (1970) suggested that selenium may be a teratogen in man from the examination of the older literature which correlated malformed babies and the consumption of toxic grains by people in Columbia.

D. Other Reproductive Effects

Vesce (1947) noted changes in endocrine glands, especially the ovaries, following oral administration of 5 to 12.5 mg sodium selenide to guinea pigs over two periods of 20 days.

E. Chronic Toxicity

Chronic effects from prolonged feeding of diets containing added selenium in amounts of 5 to 15 µg/g include liver damage in the form of atrophy, necrosis, cirrhosis, and hemorrhage, and marked and progressive anemia in some species (Fishbein, 1977). In man hepatic necrosis has not been observed following chronic exposure; however, lassitude, loss of hair, discoloration and loss of fingernails were symptoms (Beath, 1962).

F. Other Relevant Information

The essentiality of selenium for several animals has been known since the 1950's (Ganther, 1970; Schwarz, 1961) with selenium deficiency resulting in white muscle disease in ruminants, hepatic degeneration and peridontal disease in other mammals.

Synergism/antagonism exists between the actions of selenium and other metals such as arsenic, mercury, cadmium, silver and thallium (Diplock, 1976).

V. AQUATIC TOXICITY

A. Acute Toxicity

Cardwell, et al. (1976) exposed 6 species of freshwater fish to selenium dioxide and observed the 96-hour LC_{50} values to range from 2,060 to 28,500 µg/l. The 96-hour LC_{50} values for fathead minnow fry and juveniles are 2,060 and 5,200 µg/l, respectively, indicating an apparent decrease in toxicity with age. With the invertebrates Daphnia magna and scud, the LC_{50} values are 430 and 318 µg/l respectively (U.S. EPA, 1978; Adams, 1976).

The 96-hour LC_{50} values for marine species are 6,710 µg/l for the sheephead minnow (U.S. EPA, 1978) and 600 µg/l for mysid shrimp (U.S. EPA, 1978).

B. Chronic Toxicity

No pertinent data are available on the chronic toxicity of selenium to freshwater organisms (U.S. EPA, 1979). The only data available in marine species is that of the mysid shrimp (Mysidopsis bahia). It has been exposed to selenium for its life cycle and the chronic value is 135 µg/l.

C. Plant Effects

Selenium is toxic to two freshwater algal species, Chlorella vulgaris and Haematoccus cupensis, with growth being retarded at 50 µg/l (Hutchinson and Stokes, 1975). For the saltwater alga, Skeltonema costatum, the 96-hour EC_{50} values for

chlorophyll a and cell numbers are 7,930 and 8,240 µg/l, respectively (U.S. EPA, 1978).

D. Residues

Bioconcentration factors have been determined for the rainbow trout, fathead minnow and bluegill. These factors range from 2 to 20 (Adams, 1976; U.S. EPA, 1978). The tissue half-life for the bluegill is between 1 and 7 days (U.S. EPA, 1978). These results show that tissue accumulation of selenium should not present a hazard to freshwater aquatic organisms.

No residue data are available for marine species (U.S. EPA, 1979).

VI. EXISTING GUIDELINES

A. Human

The U.S. Environmental Protection Agency (1975b) has established the maximum permissible level of selenium at 0.01 mg/l for U.S. drinking waters. A time-weighted average concentration threshold limit value (TLV) of 0.2 mg/m^3 has been established by the American Conference of Government Industrial Hygienists (ACGIH, 1977). The minimum toxic dose for selenium has been calculated to be 16.1 mg/day. The U.S. EPA (1979) draft water criterion for selenium is 10 µg/l. As a result of public comments received, additional review and consideration of the recommended criterion is required.

B. Aquatic

For selenium in freshwater, the draft criterion to protect aquatic life is 9.7 µg/l as a 24-hour average and the concentration should not exceed 22 µg/l at any time (U.S. EPA, 1979). In saltwater the criterion is 4.4 µg/l as a 24-hour average and the concentration should not exceed 10 µg/l at any time.

SELENIUM

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No. 154

Silver

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

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154-2

SILVER

SUMMARY

While metallic silver in the zero valence state is not considered to be toxic, most of its salts are toxic to a large number of organisms. Silver salts can combine with certain biological molecules and subsequently alter their properties. Upon ingestion, many silver salts are absorbed in the human circulatory system and deposited in various body tissues, resulting in generalized or sometimes localized gray pigmentation of the skin and mucous membranes known as argyria. Silver has not been shown to be a carcinogen (except by the mechanism of solid state tumorigenisis); however, there is some evidence that silver salts can effect the growth of tumors. The acceptable daily intake for silver has been determined to be 1.6 mg per day for a 70 kg man.

Silver is acutely lethal to aquatic species in the µg/l range. In terms of acute lethality, Daphnia magna appears to be the most sensitive species, with a 48-hour EC_{50} of 1.5 µg/l. At levels as low as 0.17 µg/l, silver caused premature egg hatching and reduced fry growth in fathead minnows.

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SILVER

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Silver (U.S. EPA, 1979).

Silver (Ag; atomic weight 107.87) is a white ductile metal occuring naturally in the pure form and in ores. Silver can exist in two valence states, Ag^{+} and Ag^{++}. The solubility of common silver salts varies greatly, with silver nitrate having a solubility of 2.5×10^{9} µg/l and silver iodide having a solubility of 30 µg/l (Windholz, 1976). Many silver salts are light-sensitive. Water or atmospheric oxygen have no effect on metallic silver; however, ozone, hydrogen sulfide, and sulfur react with it. The principle uses of silver are in photographic materials, electroplating, dental alloys, solder and brazing alloys, paints, jewelry, silverware, coinage, mirror production.

II. EXPOSURE

Exposure to silver is mainly through food and water intake with only minimal contribution from ambient aerosols. Concentrations of silver in surface waters have been shown to vary from 0 - 38 µg/l with a mean of 2.6 µg/l in samples containing silver. High silver concentrations are obtained in high silver mineralized areas or in waters receiving effluent from industries that use silver.

The average intake of silver from food has been calculated to be 40 µg/day (Tipton, et al. 1966) to 88 µg/day (Kehoe, et al. 1940) in the U.S. Although silver is detected in meats and vegetables, the concentrations in fish, shell-

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fish, and crustacea are greater. Marine animals accumulate silver in concentrations which are higher than their environment. This is particularly significatnt in areas such as sewage-sludge dumping sites, which contain high concentrations of silver in the sediment. The dead bodies of animals in reducing environments will contribute their silver to sediments, a major factor in the geochemical cycle of silver (Boyle, 1968).

Exposure to high levels of silver has also occurred by inhalation in specific industries (e.g., silver smelting and photography) and from mechanical uses of silver compounds. Steel mills do not seem to contribute to ambient air concentrations of silver (Harrison, et al. 1971).

III. PHARMACOKINETICS

A. Absorption

Silver may enter the body via the respiratory tract, the gastrointestinal tract, mucous membranes, or broken skin. The efficiency of absorption by any of these routes is poor. Colloidal silver given orally to rats showed two to five percent absorption by the gastrointestinal tract (U.S. EPA, 1979). Dogs receiving orally a tracer quantity of silver nitrate absorbed ten percent. It was shown in humans who accidently inhaled silver that the biological half-life of silver was about one day, probably due to rapid mucociliary clearance, swallowing, and fecal excretion (Newton and Holmes, 1966). Some absorpotion did take place since there was localization of silver in the liver, but quantification was impossible. In human burn patients treated with

silver nitrate dressing, only 0.008 percent of the silver was absorbed (U.S. EPA, 1979).

B. Distribution

The amount of silver, its chemical form, and the route by which it is administered affects the tissue content and distribution of silver within the body (Furchner, et al. 1968). Table 1 summarizes data on the distribution of silver in rats.

Table 1: Distribution of Silver in the Rat and Day 6 Following Intramuscular Injections of Different Doses of Silver (percent of dose per organ) (Scott and Hamilton, 1950).

	Dose		
	Carrier-Free	0.1 mg	1.0 mg
Percent of Dose Absorbed	92.1	63.7	53.5
Absorbed			
Heart and Lungs	0.06	0.13	0.59
Spleen	0.01	0.13	2.69
Blood	0.50	0.95	3.03
Liver	0.36	2.24	33.73
Kidney	0.07	0.92	0.63
G.I. tract	1.12	4.22	8.21
Muscle	0.27	0.56	2.39
Bone	0.18	0.35	2.20
Skin	0.24	0.67	7.39
Urine	0.64	0.88	1.82
Feces	96.56	88.95	37.33
Unabsorbed	7.9	36.3	46.5

Silver administered to other species appears to generally follow this distribution pattern.

C. Metabolism

Inhaled silver particles that are not removed from the lungs by the mucociliary reflex and coughing are probably

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phagocytized and transported via the protein fractions of the blood plasma to the liver, from which they are eventually excreted in the bile. Formation of silver selinide deposits in the liver, as well as the formation of metallic silver, silver sulfide, or silver complexes with sulfur amino acids may be a method of detoxifying silver. In the kidney, complexation with metallothionein may be another detoxification pathway (U.S. EPA, 1979).

D. Excretion

Regardless of route and chemical form of silver administered, fecal excretion always predominates over urinary excretion. Most absorbed silver is excreted into the intestines by the liver via the bile. Phalen and Morrow (1973) exposed beagle dogs to an atmosphere containing silver aerosols and showed the biological half-life to be 8.4 to 12.9 days.

IV. EFFECTS

A. Carcinogenicity

Implanted foils and disks and injected colloidal suspensions of metallic silver have been found to produce tumors or hyperplasia in several studies. These tumors may be due to the particular physical form of the metal or to its being an exogenous irritant. There is no evidence that silver or its salts produce tumors by any other mechanisms. In one study, intratumoral injections of colloidal silver appeared to stimulate cancer growth (Guyer and Mohs, 1933), and in another study silver nitrate appeared to act as a promoter with DMBA (7,12-dimethylbenz(a)anthracene) initiated mice

(Saffrotti and Shubik, 1963). On the other hand, Taylor and Carmichael (1953) showed a tumor growth inhibitor effect of silver chloride. The evidence for any carcinogenic effect of silver is very tenuous (U.S. EPA, 1979).

B. Mutagenicity

Silver nitrate (Demerec, et al. 1951), silver chloride (Nishioka, 1975), and silver sulfadiazine (Fox, et al. 1969) have been examined for mutagenicity in microorganisms and shown to be nonmutagenic in these test systems.

C. Teratogenicity

Few associations between silver and birth defects have appeared in the literature and one is apparently erroneous. Kukizaki (1975) found only weak cytotoxic effects when silver-tin alloy powder was incubated in seawater with fertilized eggs or early embryos of the sea urchin Hemicentrotus pulcherrimus. Silver salts were tested for toxicity to 4- and 8-day-old chick embryos but did not produce abnormalities in development (Ridgway and Karnofsky, 1952).

D. Other Reproductive Effects

Pertinent information could not be located in the available literature concerning any other reproductive effects due to exposure to silver.

E. Chronic Toxicity

In rats, chronic exposure to 0.4 mg/l of silver in drinking water causes hemorrhages in the kidney. Larger doses cause changes in conditioned-reflex activity, lowering of immunological resistance (0.5 mg/l), and growth depression (20 mg/l). In humans, the most common noticeable effect of

chronic exposure to silver or silver compounds is generalized argyria (generalized gray pigmentation).

F. Other Relevant Information

Silver exhibits antagonism to selenium, vitamin E, and copper, inducing deficiency symptoms in animals fed adequate diets or aggravating deficiency symptoms when the animal's diet lacks one or more of the nutrients. The effects have been described in dogs, sheep, pigs, rats, chicks, turkey, poults, and ducklings (U.S. EPA, 1979).

V. AQUATIC TOXICITY

A. Acute Toxicity

Davies, et al. (1978) conducted 96-hour tests with rainbow trout in both hard (350 mg/l as $CaCO_3$) and soft water (26 mg/l as $CaCO_3$) water. The LC_{50} values were 6.5 and 13 µg/l for soft and hard water, respectively. There are too few data to assess the relative importance of hardness and experimental variability on these nonreplicated results.

The 48-hour static EC_{50} for Daphnia magna in soft water (40 mg/l as $CaCO_3$) is 1.3 µg/l (U.S. EPA, 1978), indicating that this species is the most sensitive freshwater invertebrate species tested.

Acute toxicity data are available only for four saltwater invertebrate species and range from 5.8 to 262 µg/l (Calabrese, et al. 1973; Calabrese and Nelson, 1974; Nelson, et al. 1976; Sosnowski and Gentile in: U.S. EPA, 1979). The American oyster is the most sensitive saltwater species tested, and the mysid shrimp is the most resistant.

B. Acute Toxicity

Davies, et al. (1978) conducted an 18-month mortality test with rainbow trout and found the no-effect concentration of silver to be 0.09 - 0.17 µg/l (17.2% mortality at 0.17 µg/l and no mortality at 0.09 µg/l). There was also premature hatching of eggs and reduced growth of fry at 0.17 µg/l.

The chronic toxicity of silver to mysid shrimp has been determined based on a flow-through, life-cycle exposure (Sosnowski and Gentile in: U.S. EPA, 1979). No spawning occurred at 103 µg/l. The time of spawning was delayed to seven days at 33.3 µg/l. Brood size was statistically smaller at 33.3 µg/l when compared to the controls, although larval survival was not affected. The highest concentration of silver tested that had no effect on growth, reproduction, or survival was 10.2 µg/l, which is approximately 0.04 times the 96-hour LC_{50} determined for adult shrimp.

C. Plant Effects

Hutchinson and Stokes (1975) observed growth retardation in the freshwater alga, Chlorella vulgaris, at silver concentrations between 10 and 60 µg/l. A concentration of 2,000 µg/l was determined to be toxic to six additional algal species (Gratteau, 1970).

The only marine algal species tested, Skeltonema costatum, showed growth inhibition after a 96-hour exposure to 130 µg/l (U.S. EPA, 1978).

D. Residues

Bioconcentration factors of 17 to 368 were determined for three species of insects exposed to silver

(Nehring, 1973). Bluegills showed no bioconcentration of silver at a water concentration of 0.03 µg/l after a 28-day test (U.S. EPA, 1978). Pertinent information on residues in saltwater species could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A. Humans

Both the U.S. standard for silver in drinking water and in workplace air have been based on a presumed 1 g minimum dose of silver that has caused agryia.

The existing standards for silver are:

Existing Standards Regarding Silver

Medium	Silver Concentration	Authority
Drinking water	50 µg/l	U.S. EPA (1976);National Academy of Sciences (1977)
Drinking water	0.5 µg/l	State of Illinois (cited in National Academy of Sciences,1977)
Drinking water	10 µg/l	State of California (cited in National Academy of Sciences, 1977)
Workplace air, threshold limit value time-weighted	0.01 mg/m^3	Occupational Safety and Health Administration (1974) (39 FR 23541)
Short-term exposure limit ($\geq$ 15 minutes) 4 times per day	0.03 mg/m^3	American Conference of Governmental Industrial Hygiensts (1977)

The acceptable daily intake (ADI) for silver is 1.6 mg/day. The U.S. EPA draft water criterion for silver is 10 µg/l for the protection of human health. This criterion is presently

undergoing further evaluation and review before final recommendation.

B. Aquatic

For silver the draft criterion to protect freshwater aquatic life is 0.009 µg/l as a 24-hour average; the concentration should not exceed 1.9 µg/l at any time (U.S. EPA, 1979).

To protect saltwater aquatic life, the draft criterion is 0.26 µg/l as a 24-hour average; the concentration should not exceed 0.58 µg/l at any time (U.S. EPA, 1979).

SILVER

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No. 155

TCDD

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (TCDD)

SUMMARY

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) has been found to induce heptocellular carcinomas and tumors in two rat feeding studies. TCDD has also produced fetotoxic and teratogenic effects in laboratory animals. The positive mutagenicity of TCDD has been demonstrated in three bacterial bioassay systems. TCDD is also a potent inducer of hepatic and renal microsomal drug metabolizing enzymes.

No standard tests for acute or chronic toxicity in aquatic life have been conducted with TCDD. Other studies, however, have shown adverse effects over a period of 96 hours to concentrations as low as 0.000056 µg/l. The weighted average bioconcentration factor for TCDD for edible portion of all aquatic organisms consumed by Americans has been calculated to be 5,800.

2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (TCDD)

I. INTRODUCTION

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is a contaminant unintentionally formed during the production of 2,4,5-trichlorophenol (TCP) from 1,2,4,5-tetrachlorobenzene. TCDD is also found as a contaminant of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) (U.S. EPA, 1979).

Characteristically, TCDD ($C_{12}H_4Cl_4O_2$) is a white crystalline solid with the following physical properties: melting point, 302-305°C; solubility in water, 0.2 to 0.6 µg/l; lipiphilic, and non-volatile (U.S. EPA, 1979).

TCDD is considered a relatively stable compound which can be degraded at temperatures in excess of 500°C, or by irradiation with UV light or sunlight under certain conditions (U.S. EPA, 1979). It has been shown to disappear slowly from soil with residues persisting for ten years after application. TCDD bio-accumulates in aquatic organisms.

II. EXPOSURE

A. Water

The amount of human exposure that can be directly attributed to drinking water alone is difficult to determine (U.S. EPA, 1979). It has been stated that no TCDD has ever been detected in drinking water, with limits of detection in the parts per trillion range (National Research Council, 1977). Underground water supplies would probably not be contaminated with TCDD under most conditions since vertical movement of TCDD has not been demonstrated in soil (Kearney, et al., 1972).

B. Food

The occurence of TCDD in food could result from (1) accidental spraying of plant crops; (2) contaminated forage or (3) food chain magnification (U.S. EPA, 1979).

TCDD is neither absorbed by oat and soybean seeds after spraying, nor taken up from the soil into the mature plants (Isensee and Jones, 1971; Matsumura and Benezet, 1973). Aqueous solutions of pure TCDD exposed to either artificial light or sun light, do not decompose, whereas TCDD photodecomposes rapidly when applied to leaf surfaces as a contaminant of the herbicides Agent Orange and Esteron (Crosby, et al., 1971; Crosby and Wong, 1977).

TCDD has been detected in the adipose tissue of cattle feeding on contaminated forage (Kocher, et al., 1978). Studies conducted for the U.S. EPA also found TCDD in fat of cattle previously exposed to 2,4,5-T (U.S. EPA, 1979). No TCDD, however, was detected in liver samples.

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor of TCDD at 5,800. This estimate is based on measured steady state bioconcentration studies in channel catfish containing 3.2 percent lipids (Isensee and Jones, 1975).

C. Inhalation

Pertinent information could not be located in the available literature.

III. PHARMACOKINETICS

A. Absorption

Approximately 83-86 percent of the TCDD administered in a single oral dose, following activation with multiple oral doses, is absorbed from the intestinal tract (Rose, et al., 1976).

B. Distribution

The excretion of a single oral dose of TCDD in rats occurred via the feces (53 percent), urine (13 percent), and expired air (two percent) (Piper, et al., 1973). Analysis after three days showed the highest percent of the administered dose per gram in the liver (3.18 percent) and adipose (2.60 percent).

Rose, et al. (1976) found that 22 days after a single oral dose of ^{14}C labeled TCDD, 1.26 and 1.25 percent of the ^{14}C was retained per gram of liver and adipose tissue, respectively. After repeated oral doses, however, the liver was found to have five times as much radioactivity as adipose tissue. Single oral doses of TCDD were excreted through the feces, whereas significant amounts of radioactivity were found both in the urine and the feces after repeated oral doses.

C. Metabolism

There is no complete agreement as to whether or not TCDD is actually metabolized (U.S. EPA, 1979). Rose, et al. (1976) found unchanged ^{14}C-labeled TCDD in the liver after oral administration, but noted that most of the radio-

activity in the feces came from compounds other than TCDD. The slow elimination of TCDD from rats and monkeys suggests that it is not readily metabolized (Van Miller, et al., 1976).

D. Excretion

See also section B., Distribution.

Differences in TCDD elimination have been observed between the sexes and between species. Rose, et al. (1976) found male rats excreted 3.1 percent of the cumulative dose in the urine while females excreted 12.5 percent in the urine.

The half-life of radioactive TCDD following a single oral dose to rats was 31 $\pm$ 6 days, while that following repeated oral doses was 23.7 days (Rose, et al., 1976).

IV. EFFECTS

A. Carcinogenicity

Three studies have reported data concerning the carcinogenicity of TCDD. Van Miller, et al. (1977) fed rats dietary levels of TCDD ranging from 0.001 to 1000 µg/kg of diet for up to 78 weeks. In 50 animals receiving diets ranging from 0.005 µg/kg to 5 µg/kg 13 benign and 15 malignant tumors were observed. No tumors were found in controls or those fed a dietary level of 0.0001 µg/kg. Animals fed diets of 50 µg/kg or more died between the second and fourth week of treatment.

Toth, et al. (1977) administered TCDD to mice at levels of 0.007, 0.7, and 7 µg/kg per week for 12 months. No tumors were noted at any dose.

Kociba, et al. (in press) administered 0.1, 0.01, and 0.001 µg/kg ofTCDD per kg of body weight to male and female rats. Males at the 0.1 µg/kg dose exhibited a statistically significant increased incidence of squamous cell carcinomas of the hard palate (4 out of 50) and of the tongue (3 out of 50). No carcinomas were observed in the male controls (0 out of 85). Females at the 0.1 µg/kg dose had a statistically significant increase in incidence of carcinomas at three sites: squamous cell carcinoma of the hard palate (4 out of 49), squamous cell carcinoma of the lung (7 out of 40), and hepatocellular carcinoma of the liver (11 out of 49). Only one carcinoma of these three sites occurred in the female controls (1 out of 86), and that was hepatocellular carcinoma of the liver. Five sites, pancreas, adrenal gland, pituitary gland, uterus, and mammary gland, had a statistically significant decrease in their tumor incidence at certain dose levels (Kociba, et al., in press).

B. Mutagenicity

Multiple oral doses of TCDD over 6 weeks resulted in vacuolization of liver cell nuclei, increased mitotic rate, and a polyploid chromosome number (Vos, et al., 1974).

TCDD administered by intubation intraperitonealy, or orally did not cause chromosomal aberrations in bone marrow cells (Green and Moreland 1975). However, repeated dosing of TCDD over 13 weeks produced an increase in chromosomal breaks in rat bone marrow (Green, et al. 1977).

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Some studies have been conducted showing that TCDD might be a dominant lethal inducing agent, while others have found no evidence of this effect (U.S. EPA, 1979).

Bacterial assays with E. coli, and S. typhimurium have found TCDD to be mutagenic via intercalation with DNA (Hussain, et al., 1972). Some strains of Salmonella, however, have yielded negative mutagenic results when tested (Seiler, 1973).

Tenchini, et al. (1977) found no significant differences in chromosome number or chromosomal abnormalities in maternal or abortive fetal samples from pregnant women exposed to TCDD during the explosion of a 2,4,5-T factory in Italy.

C. Teratogenicity

Teratogenic effects from TCDD have been reported in several studies. Both teratogenic and fetotoxic effects were observed in mice and rats administered 2,4,5-T containing 30 ppm TCDD (Courtney, et al., 1970). Smith, et al. (1976) found the incidence of cleft palate to be significantly higher in mice receiving 1 µg/kg and 3 µg/kg per day of TCDD for 10 days during gestation. At 3 µg/kg, the incidence of bilateral dilated renal pelvis among fetuses was also significantly greater. TCDD levels of 0.125 to 2.0 µg/kg/day given orally to rats on days 6 to 15 of gestation produced dose-related increases in fetal mortality, fetal intestinal hemorrhages, and early and late resorptions (Sparschu, et al., 1971).

D. Other Reproductive Effects

Pertinent information could not be located in the available literature.

E. Chronic Toxicity

Chronic studies involving administration of TCDD to rats, guinea pigs and mice, have reported toxic effects to the liver and thymus (U.S. EPA, 1979). Female rhesus monkeys fed a diet containing 500 ppt TCDD for up to nine months, exhibited symptoms of facial hair and eyelash loss, edema, accentuated hair follicles, and dry scaly skin (Allen, et al., 1977).

A large number of studies have reported the incidence of chloracne among workers exposed to TCDD during the production of 2,4,5-trichlorophenol (TCP, 2,4-D or 2,4,5-T) (U.S. EPA, 1979). Other chemical manifestations among exposed workers include muscular weakness, loss of appetite and weight, sleep disturbances, orthostatic hypotension, abdominal pain, liver impairment, hyperpigmentation of the skin, hirsutism, and psychopathological changes (U.S. EPA, 1979).

F. Other Relevant Information

No synergistic effect was detected when 2,4,5-T and TCDD were administered to mice alone, or in combination with each other (U.S. EPA, 1979). Both compounds are capable of producing cleft palates and kidney anomalies in fetuses.

The International Agency for Research on Cancer (1977) has reviewed the literature and concludes that TCDD is a potent inducer of hepatic and renal microsomal drug

metabolizing enzymes. TCDD intoxication results in a marked increase in the cellular smooth endoplasmic reticulum content of hepatic and renal cells. This compound is also capable of simultaneously activating and suppressing certain microsome associated foreign compound and steroid-hormone-metabolizing enzyme systems. It has been found to increase the activity of renal and hepatic glutathione-S-transferase, and hepatic δ-aminolevulinic acid (ALA) synthetase and arylhydrocarbon hydroxylase (AHH).

V. AQUATIC TOXICITY

A. Acute toxicity

Miller, et al. (1973) exposed coho salmon (Oncorhynchus kisutch) to aqueous concentrations of TCDD at 0.000056, 0.0056, or 0.056 µg/l for 24-96 hours under static conditions, then transferred these fish to control water. After 60 days 12 and 55 percent mortalities were observed in the low and intermediate dose groups, respectively. Coho salmon exposed to the high dose for 24 hr were all dead within 40 days. The corresponding mortality for control fish at 60 days was 2 percent.

B. Chronic Toxicity

Pertinent information could not be located in the available literature.

C. Plant Effects

Pertinent information could not be located in the available literature.

D. Residues

TCDD has a high affinity for the tissues of aquatic species. Isensee and Jones (1975) conducted a model freshwater ecosystem study on TCDD and observed bioconcentration factors between 3,600 and 26,000 over a 3 to 31 day period. The highest bioconcentration factors were reported for Dyphnia magna (26,000), the mosquito fish, Gambusia affinis (25,000), and the snail, Physa sp. (20,000).

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The calculated acceptable daily intake (ADI) for TCDD is 10^{-4} µg/kg/day. This ADI does not consider TCDD to be a known or suspected carcinogen (NRC, 1977).

The draft ambient water quality criterion has been set by the U.S. EPA (1979) at levels intended to reduce the human carcinogenic risk to rhe range of 10^{-5}, 10^{-6}, and 10^{-7}. The corresponding draft criteria are 4.55×10^{-7} µg/l, 4.55×10^{-8} µg/l, and 4.55×10^{-9} µg/l, respectively.

B. Aquatic

No drafted criterion is available to protect fresh and saltwater species from TCDD toxicity.

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No. 156

1,1,1,2-Tetrachloroethane

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

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SUMMARY

1,1,1,2-Tetrachloroethane is potentially formed during chlorination of drinking water and has been identified at a concentration of 0.11 µg/l. Although inhalation is the major route of exposure to chlorinated ethanes, specific information on 1,1,1,2-tetrachloroethane inhalation is not available.

Literature reporting adverse occupational exposures to this chloroethane cannot be found. Animal experiments measuring the acute and subacute effects indicate, however, that chronic exposure may produce liver damage. 1,1,1,2-Tetrachloroethane is currently being tested by the National Cancer Institute for possible carcinogenicity. The compound not mutagenic according to one report. Data could not be located in the available literature showing it to be teratogenic.

Pertinent information could not be found in the available literature regarding the adverse effects of this compound on aquatic animals or plants.

1,1,1,2-TETRACHLOROETHANE

I. INTRODUCTION

This profile is based primarily on the Ambient Water Quality Criteria Document for Chlorinated Ethanes (U.S. EPA, 1979a).

The chloroethanes are hydrocarbons in which one or more of the hydrogen atoms of ethane are replaced by chlorine atoms. In general, water solubility and vapor pressure decrease with increasing chlorination, while density and melting point increase. 1,1,1,2-Tetrachloroethane (molecular weight 167.9) is a liquid at room temperature with a boiling point of 129°C, a melting point of -68°C, a specific gravity of 1.553, and a solubility in water of 2.85 mg/l (U.S. EPA, 1979a).

1,1,1,2-Tetrachloroethane is used as a solvent and in the manufacture of a number of widely used products, as are the other chloroethanes (U.S. EPA, 1975). In general, these compounds form azeotropes with water (Kirk and Othmer, 1963) and are very soluble in organic solvents (Lange, 1956). Pearson and McConnell (1975) were unable to demonstrate microbial degradation of these compounds, but did report chemical degradation. For a more general treatment of the chlorinated ethanes as a class, the reader is referred to the EPA/ECAO Hazard Profile on Chlorinated Ethanes (U.S. EPA, 1979b).

II. EXPOSURE

1,1,1,2-Tetrachloroethane is potentially formed during chlorination of drinking water and has been identified at a concentration of 0.11 µg/l (U.S. EPA, 1974). Information on the levels of 1,1,1,2-tetrachloroethane in food are not available although other chloroethanes have been detected (U.S. EPA, 1979a). Inhalation is the major route of exposure to chlorinated ethanes. However, specific information on 1,1,1,2-tetrachloroethane exposure is not

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available (U.S. EPA, 1979a). As with most solvents, chloroethanes can be absorbed through the skin. This is not, however, a major route of exposure (U.S. EPA, 1979a).

The U.S. EPA (1979a) has estimated a weighted average bioconcentration factor of 18 for 1,1,1,2-tetrachloroethane for the edible portions of fish and shellfish consumed by Americans. This value was based on an estimated steady-state bioconcentration factor of 62, which was determined from an octanol/water partition coefficient of 457.

III. PHARMACOKINETICS

A. Absorption

Specific information on the absorption of 1,1,1,2-tetrachloroethane is not available. In general, the chloroethanes are absorbed rapidly following ingestion or inhalation (U.S. EPA, 1979a).

B. Distribution

Inhalation or ingestion of 1,1,1,2-tetrachloroethane results in the presence of high levels of solvent in the fetuses of the exposed animals (Truhaut, et al. 1974). Other studies indicate a widespread distribution of chloroethanes throughout the body after administration (U.S. EPA, 1979a).

C. Metabolism

After oral administration to rats, guinea pigs, and rabbits, 1,1,1,2-tetrachloroethane underwent hydrolytic dehalogenation resulting in formation of trichloroethanol, which was eliminated primarily in the urine in the form of a conjugated glucuronic derivative, urochloralic acid. Oxidation to trichloroacetic acid was considerable only in rats (Nguyen, et al. 1971; Truhaut and Nguyen, 1973). In the latter study monochloroacetic acid and mercaptan derivatives were not found in the urine. The only halogenated

compound found in the expired air was untransformed 1,1,1,2-tetrachloroethane. Trichloroethanol and trichloroacetic acid have also been identified in the urine of rats following interperitoneal (i.p.) injection or vapor inhalation of 1,1,1,2-tetrachloroethane (Ikeda and Ohtsuji, 1972), and have been identified in the urine of mice following i.p. injection of the parent compound (Yllner, 1971).

In general, the metabolism of chloroethanes involves both enzymatic dechlorination and hydroxylation and non-enzymatic oxidation (U.S. EPA, 1979a). Oxidation reactions may produce unsaturated metabolites which are then transformed to the alcohol and ester (Yllner, 1971).

D. Excretion

Murine studies show that, after i.p. injection of 1,1,1,2-tetrachloroethane, approximately 78 percent of the dose is excreted in 72 hours; from 21 to 62 percent of this dose is excreted in the breath and from 18 to 56 percent as metabolites in the urine (Yllner, 1971). Other studies also indicate that 1,1,1,2-tetrachloroethane is excreted in the urine as metabolites and in the expired breath as the parent compound (see above).

IV. EFFECTS

A. Carcinogenicity

1,1,1,2-Tetrachloroethane is currently being tested by NCI for possible carcinogenicity; results are not available (NTCTP, 1980). Other information relative to the potential carcinogenicity of 1,1,1,2-tetrachloroethane was not located in the available literature.

B. Mutagenicity

Simmon, et al. (1977) tested 71 chemicals identified in the U.S. drinking water for mutagenesis with an Ames Salmonella/microsome assay. 1,1,1,2-Tetrachloroethane was found not to be mutagenic in this study.

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C. Teratogenicity and Other Reproductive Effects

The isomer of 1,1,1,2-tetrachloroethane, syn-tetrachloroethane, is a weak teratogen in two strains of mice (Schmidt and Reiner, 1976). Both tetrachloroethanes are embryotoxic (Schmidt and Reiner, 1976; Truhaut, et al., 1974). Other pertinent data have not been found.

D. Chronic Toxicity

Adverse occupational exposure to 1,1,1,2-tetrachloroethane has not been reported by NIOSH. (U.S. EPA, 1979a). Animal experiments measuring acute and subacute effects indicate that chronic inhalation exposure may produce liver damage (see below).

E. Acute and Subacute Toxicities

At 24 hours after the oral administration of 0.5 g 1,1,1,2-tetrachloroethane/kg to rabbits, the blood cholesterol and total lipid levels were increased and the glutamic-pyruvic transaminase, glutamic-oxalacetic transaminase, creatine phosphokinase, lactate dehydrogenase, and a-hydroxybutyrate dehydrogenase activities were enhanced. Except for creatine phosphokinase, these enzyme levels remain elevated at 72 hours after poisoning (Truhaut, et al. 1973). Subsequent studies by this research group found that in rabbits, 1,1,1,2-tetrachloroethane was only slightly irritating to the skin and ocular mucous membrane, and its cutaneous LD_{50} was 20 g/kg. Its acute toxicity by inhalation, for an exposure of 4 hours, was similar in rats and rabbits, with the LC_{50} being 2500 mg/m^3. The oral LD_{50} values in rats and mice were 800 and 1500 mg/kg, respectively. Histological examination revealed hepatotoxic activity, including formation of microvacuolizations and centrolobular necrosis. 1,1,1,2-Tetrachloroethane was from two to three times less toxic than 1,1,2,2-tetrachloroethane (Truhaut, et al. 1974).

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Recent studies exploring subacute effects indicate that in female Wistar rats, 1,1,1,2-tetrachloroethane (0.30 g/kg, 5 days/week, for 2 weeks, orally) induced hepatic steatosis by accumulation of triglycerides, accompanied by a decrease in liver lactate dehydrogenase, malate dehydrogenase, and glutamic pyruvic transaminase activities. The tetrachloroethane caused no changes in the liver of male rats (Truhaut, et al. 1975). However, another team of investigators found that 1,1,1,2-tetrachloroethane (from 100 to 800 μmoles/kg/day for 7 days, i.p.) to male rats increased liver succinate dehydrogenase, acid phosphatase and glucose 6-phosphatase activities and decreased liver DNA content. In addition, the white cell count was increased and the red cell count and blood cholesterol content were decreased (Chieruttini, et al. 1976).

V. AQUATIC TOXICITY

Pertinent data could not be located in the available literature regarding either the acute and chronic toxicity to aquatic animals, or the aquatic residues of 1,1,1,2-tetrachloroethane.

VI. EXISTING GUIDELINES AND STANDARDS

Guidelines for occupational exposure to 1,1,1,2-tetrachloroethane do not exist (International Labor Office, No. 37, 1977; NIOSH, 1978); however, 1,1,2,2-tetrachloroethane exposure is limited in the workplace to 5 ppm (35 mg/cu m) as an 8-hour time-weighted average (TWA) concentration.

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No. 157

1,1,2,2-Tetrachloroethane

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated 1,1,2,2,-tetrachloroethane and has found sufficient evidence to indicate that this compound is carcinogenic.

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1,1,2,2-TETRACHLOROETHANE

SUMMARY

An increased incidence of hepatocellular carcinomas has been shown in mice following oral administration of 1,1,2,2-tetrachloroethane. Mutagenic effects have been reported in the Ames Salmonella assay and in E. coli. There is no available evidence to indicate that 1,1,2,2-tetrachloroethane produces teratogenic effects. Occupational exposure to 1,1,2,2-tetrachloroethane has produced several toxic effects including neurological symptoms, liver and kidney damage, pulmonary edema, and fatty degeneration of heart muscle.

The toxicity of 1,1,2,2-tetrachloroethane has been examined in one species each of freshwater and marine fish, invertebrates, and plants. Freshwater invertebrates appear to be the most sensitive species examined, with acute toxic concentrations of 9,320 µg/l being reported.

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1,1,2,2-TETRACHLOROETHANE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Chlorinated Ethanes (U.S. EPA, 1979a).

The chloroethanes are hydrocarbons in which one or more of the hydrogen atoms of ethane are replaced by chlorine atoms. In general, water solubility and vapor pressure decrease with increasing chlorination, while density and melting point increase. 1,1,2,2-Tetrachloroethane (molecular weight 167.9) is a liquid at room temperature with a boiling point of 146.3°C, a melting point of -36°C, a specific gravity of 1.596, and a solubility in water of 2.9 gm/l (U.S. EPA, 1979a).

The chloroethanes are used as solvents, cleaning and degreasing agents, and in the chemical synthesis of a number of compounds.

The chlorinated ethanes form azeotropes with water (Kirk and Othmer, 1963). All are very soluble in organic solvents (Lange, 1956). Microbial degradation of the chlorinated ethanes has not been demonstrated (U.S. EPA, 1979a). For additional information regarding the chlorinated ethanes in general, the reader is referred to the Hazard Profile on Chlorinated Ethanes (U.S. EPA, 1979b).

II. EXPOSURE

The chloroethanes present in raw and finished waters are due primarily to industrial discharges. Small amounts of chloroethanes may be formed by chlorination of drinking water or treatment of sewage. Atmospheric chloroethanes result

from evaporation of volatile chloroethanes during use as degreasing agents or in dry cleaning operations (U.S. EPA, 1979a).

Routes of human exposure to chloroethanes include water, air, contaminated foods and fish, and dermal absorption. Fish and shellfish have shown levels of chloroethanes in the nanogram range (Dickson and Riley, 1976). Information on the levels of 1,1,2,2-tetrachloroethane in foods is not available.

The EPA (1979a) has estimated a weighted average bioconcentration factor for 1,1,2,2-tetrachloroethane to be 18 for the edible portions of fish and shellfish consumed by Americans. This estimate was based on steady-state bioconcentration studies in the bluegill.

III. PHARMACOKINETICS

A. Absorption

The chloroethanes are absorbed rapidly following ingestion or inhalation (U.S. EPA, 1979a). Morgan, et al. (1972) have determined that 1,1,2,2-tetrachloroethane has a high octanol/water partition coefficient, high rate of pulmonary absorption, and low rate of elimination by exhalation.

B. Distribution

Pertinent data could not be located in the available literature on 1,1,2,2-tetrachloroethane. The reader is referred to a more general treatment of chlorinated ethanes (U.S. EPA, 1979b), which indicates widespread distribution of these compounds throughout the body.

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C. Metabolism

The metabolism of chloroethanes involves both enzymatic dechlorination and hydroxylation and non-enzymatic oxidation (U.S. EPA, 1979a). Oxidation reactions may produce unsaturated metabolites which are then transformed to the alcohol and ester (Yllner, 1971). Trichloroethanol and trichloro acetic acid have been identified in the urine of rats following inhalation of 1,1,2,2-tetrachloroethane vapor (Ikeda and Ohtsuji, 1972). Metabolism of this compound appears to involve the activity of the mixed-function oxidase system (Van Dyke and Wineman, 1971).

D. Excretion

The chloroethanes are excreted primarily in the urine and expired air. Murine studies indicate that, after intraperitoneal (i.p.) injection of 1,1,2,2-tetrachloroethane, approximately 80 percent of the dose is excreted in 72 hours. Half of this dose is excreted as carbon dioxide in the breath and one-fourth as metabolites in the urine (Yllner, 1971). Human studies (Morgan, et al. 1972) indicate that after inhalation exposure of 1,1,2,2-tetrachloroethane the amount expired in the breath is less than that observed in animal studies, although a different radioactive tracer was used.

IV. EFFECTS

A. Carcinogenicity

Results of a National Cancer Institute (NCI) carcinogenesis bioassay for 1,1,2,2-tetrachloroethane show that oral administration produced an increased incidence of hepato-

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cellular carcinomas in exposed mice (NCI, 1978). No statistically significant tumor increase was seen in rats.

B. Mutagenicity

The mutagenic activity of 1,1,2,2-tetrachloroethane has been shown in the Ames Salmonella assay and in a DNA polymerase-deficient strain of E. coli (Brem, et al., 1974).

C. Teratogenicity and Other Reproductive Effects

Embryo toxicity and weak teratogenicity have been reported in two strains of mice exposed with 1,1,2,2-tetrachloroethane (Schmidt and Reimer, 1976). Other pertinent information could not be located in the available literature.

D. Chronic Toxicity

Occupational exposure to 1,1,2,2-tetrachloroethane has produced toxic effects including neurological symptoms, liver and kidney damage, pulmonary edema, and fatty degeneration of heart muscle (U.S. EPA, 1979a).

Animal experiments have indicated that chronic inhalation exposure may produce liver and kidney degeneration (U.S. EPA, 1979a).

V. AQUATIC TOXICITY

A. Acute Toxicity

Toxicity studies on one species from each category of freshwater and marine fish and invertebrates have been reported (U.S. EPA, 1978). In freshwater fish, the study yielded a 96-hour static LC_{50} value of 21,300 ug/l for the bluegill (Lepomis macrochirus). For freshwater invertebrates, the study yielded a 48-hour static LC_{50} value of

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9,320 µg/l for the caldoceran Daphnia magna. In marine fish and invertebrates, the studies yielded a 96-hour static LC_{50} value of 12,300 µg/l for the sheepshead minnow (Cyprinodon variegatus), and of 9,020 µg/l for the mysid shrimp (Mysidopsis bahia).

B. Chronic Toxicity

Pertinent information could not be located in the available literature.

C. Plant Effects

When the freshwater algae Selenastrum capricornutum was tested for adverse effects of 1,1,2,2-tetrachloroethane on chlorophyll and cell numbers EC_{50} values of 136,000 and 146,000 µg/l were obtained. When the marine algae Skeletonema costatum was tested for these adverse effects, 96-hour EC_{50} values were 6,440 and 6,230 µg/l, respectively.

D. Residues

A bioconcentration value of 8 was reported for the bluegill (U.S. EPA, 1979a).

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor aquatic criteria derived by U.S. EPA (1979a), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

Based on the NCI carcinogenic data, and using a linear, nonthreshold model, the U.S. EPA (1979a) has estimated the level of 1,1,2,2-tetrachloroethane in ambient water

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that will result in an additional cancer risk of 10^{-5} to be 1.8 µg/l.

The exposure standard determined by OSHA for 1,1,-2,2-tetrachloroethane is 5 ppm as an eight-hour time-weighted average concentration.

B. Aquatic

The draft criterion for protection of freshwater aquatic life is 170 µg/l as a 24-hour average, not to exceed 380 µg/l. The draft criterion to protect marine life from 1,1,2,2-tetrachloroethane is 70 µg/l as a 24-hour average, not to exceed 160 µg/l (U.S. EPA, 1979a).

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No. 158

Tetrachloroethylene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated tetrachloroethylene and has found sufficient evidence to indicate that this compound is carcinogenic.

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TETRACHLOROETHYLENE

SUMMARY

Tetrachloroethylene is widespread in the environment, and is found in trace amounts in water, aquatic organisms, air, foodstuffs, and human tissue. Tetrachloroethylene causes mild intoxication and liver dysfunction following chronic exposure to high levels associated with certain industries. Tetrachloroethylene has not been shown to be teratogenic, but it has been shown to be mutagenic in bacterial assays and carcinogenic in mice.

The bluegill (Lepomis macrochirus) is the most sensitive freshwater species to acute tetrachloroethylene toxicity with a reported 96-hour LC_{50} of 12,900 µg/l. In the only acute toxicity study for saltwater species the mysid shrimp (Mysidopsis bahia) has an observed 96-hour LC_{50} value of 10,200 µg/l. The chronic value for this shrimp is 448 µg/l. A freshwater algae has a reported no-effect concentration of tetrachloroethylene at 816,000 µg/l. A marine alga, however, was adversely affected at the considerably lower level of 10,000 µg/l. Tetrachloroethylene is only slightly bioconcentrated by the bluegill (49 times) after 21 days of exposure, and has an elimination half-life of less than one day.

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I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Tetrachloroethylene (U.S. EPA, 1979).

Tetrachloroethylene (C_2Cl_4, 1,1,2,2-tetrachloroethylene, perchloroethylene, PCE; molecular weight 165.85) is a colorless, nonflammable liquid. It has the following physical/chemical properties (Patty, 1963):

Melting Point:	-23.25°C
Density:	1.623 g/ml
Vapor Pressure:	19 mm Hg
Water Solubility:	150 ug/ml
Octanol/Water Partition Coefficient:	339

Tetrachloroethylene is primarily used as a solvent in the dry cleaning industry and, to a lesser extent, as a degreasing solvent in metal industries (Windholz, 1976).

II. EXPOSURE

The National Organics Monitoring Survey (U.S. EPA, 1978) detected tetrachloroethylene in 9 out of 105 drinking water samples between November 1976 and January 1977 (range, <0.2 to 3.1 ug/l; median <0.2 ug/l). No data exist for ingestion of tetrachloroethylene from food for the United States. However, in England, tetrachloroethylene concentrations in foods ranged from nondetectable amounts in orange juice to 13 ug/kg in butter (McConnel, et al., 1975). The U.S. EPA (1979) has estimated the weighted bioconcentration factor of tetrachloroethylene to be 110 for the edible portion of consumed fish and shellfish. This estimate is based on measured steady-state bioconcentration studies in bluegills. Generally,

environmental tetrachloroethylene concentrations in air tend to be low. A survey of eight locations in the U.S. indicated concentrations up to 6.7 $\mu g/m^3$ in urban areas and less than 0.013 $\mu g/m^3$ in rural areas (Lillian, et al., 1975). By far the most significant exposure to tetrachloroethylene is in the industrial environment (Fishbein, 1976). Significant dermal exposure would be confined to occupational settings.

III. PHARMACOKINETICS

A. Absorption

Using inhalation exposure, Stewart, et al. (1961) found that tetrachloroethylene reached near steady-state levels in the blood of human volunteers with two hours of continuous exposure. However, steady-state conditions in this study were probably obtained by a redistribution phenomenon, since the biological half-life of tetrachloroethylene metabolites in humans has been measured to be 144 hours (Ikeda and Imamura, 1973).

B. Distribution

In humans (McConnell, et al., 1975) and rats (Savolainen, et al., 1977), tetrachloroethylene tends to accumulate in the body fat, and to a lesser extent in the brain and liver. Measurements in the rat suggests that the level of PCE in the liver and blood remains constant after three hours of exposure.

C. Metabolism

In a qualitative sense, metabolic products appear to be similar in humans (Ikeda, et al., 1972; Ikeda, 1977) and experimental animals (Yllner, 1961; Daniel, 1963; Ikeda

and Ohtsuji, 1972). The metabolism of tetrachloroethylene leads to the production of trichloroacetic acid, and is apparently saturable (Ikeda, 1977). The enzyme systems responsible for this metabolism are inducible with phenobarbital (Ikeda and Imamura, 1973) and polychlorinated biphenyls (Moslen, et al., 1977).

D. Excretion

In humans tetrachloroethylene is primarily eliminated from the body via the lungs with a half-life of elimination estimated to be 65 hours (Stewart, et al., 1961, 1970; Ikeda and Imamura, 1973). Its metabolite, trichloroacetic acid, is eliminated in the urine of humans with a half-life estimated to be 144 hours (Ikeda and Imamura, 1973).

IV. EFFECTS

A. Carcinogenicity

Tetrachloroethylene caused hepatocellular carcinomas in B6C3-F1 mice of both sexes (NCI, 1977). An experiment in Osborne-Mendel rats produced negative results, although early mortality precluded the use of this data in evaluating the carcinogenicity of PCE (NCI, 1977).

Greim, et al. (1975) could not demonstrate an increase in the mutation rate of E. coli K_{12} with tetrachloroethylene. However, Cerna and Kypenova (1977) tested PCE and found elevated mutagenic activity in Salmonella strains sensitive to both base pair substitution and frameshift mutations.

C. Teratogenicity

Only one report has appeared concerning possible

tetrachloroethylene-induced teratogenesis (Schwetz, et al. 1975). Female rats and mice were exposed to 2000 mg/m^3 7 hours daily on days 6 to 15 of gestation. Significant decreases in fetal body weight and resorption, subcutaneous edema and delayed ossification of skull bones and sternabone in the pups were noted. These effects were mild, however, and led the authors to conclude that PCE was not teratogenic. Additional work is necessary to determine whether PCE is teratogenic (U.S. EPA, 1979).

D. Other Reproductive Effects

No information available.

E. Chronic Toxicity

Repeated exposure to tetrachloroethylene has resulted in damge to liver and kidney in dogs (Klaassen and Plaa, 1967). Toxic nephropathy has also been observed in mice and rats (NCI, 1977). In humans, chronic exposure to 1,890 to 2,600 mg PCE/m^3 caused three of seven men to have impaired liver function (Coler and Rossmiller, 1953). Occasional reports have even associated tetrachloroethylene exposure with the symptomatology of more serious chronic diseases such as Raynaud's disease (Lob, 1957; Sparrow, 1977). Sparrow (1977) reported a case which involved depressed immune function, mildly depressed liver function, polymyopathy and severe acrocyanosis. In a group of workers occupationally exposed to lower concentrations of tetrachloroethylene at approximately 400 mg/m^3 (one for 15 years), subjective complaints, such as headache, fatigue, somnolence, dizziness,

and a sensation of intoxication were noted (Medek and Kovarik, 1973).

F. Other Relevant Information

Intolerance of alcohol has been reported with tetrachloroethylene exposure (Gold, 1969).

V. AQUATIC TOXICITY

A. Acute Toxicity

Ninety-six hour LC_{50} values for flow-through and static tests are 18,400 and 21,400 µg/l, respectively, with the fathead minnow, Pimephales promelas (Alexander, et al. 1978). With the bluegill, Lepomis macrochirus, the 96-hour LC_{50} value is 12,900 µg/l (U.S. EPA, 1978). For Daphnia magna, an observed 48-hour LC_{50} value of 17,700 µg/l has been recorded (U.S. EPA, 1978).

No acute data are available for saltwater fish. The mysid shrimp (Mysidopsis bahia) has an observed 96-hour LC_{50} of 10,200 µg/l (U.S. EPA, 1978).

B. Chronic Toxicity

Chronic test data are not available for freshwater species. A chronic value for the saltwater mysid shrimp in a life cycle test is 448 µg/l (U.S. EPA, 1978).

C. Plant Effects

No adverse effects on chlorophyll a concentration or cell numbers with the alga, Selenastrum capricornutum, were observed at exposure concentrations as high as 816,000 µg/l (U.S. EPA, 1978). Two 96-hour EC_{50} values were reported for the marine micro alga, Skeletonema costatum: 504,000 µg/l based on cell numbers and 509,000 µg/l based on

chlorophyll a concentration (U.S. EPA, 1978). The macroalga, Phaeodectylum tricornutum, was considerably more sensitive to tetrachloroethylene toxicity with a reported EC_{50} of 10,500 µg/l (Pearson and McConnell, 1975).

D. Residues

The bioconcentration factor for bluegills, Lepomis macrochirus, has been reported to be 49 (U.S. EPA, 1978). Equilibrium was reached within 21 days and the depuration rate was rapid with a half-life of less than one day.

VI.G EXISTING GUIDLINES AND STANDARDS

A. Human

Based on the NCI mice data, and using the "one-hit" model, the U.S. EPA (1979) has estimated levels of tetrachloroethylene in ambient water which will result in specified risk levels of human cancer:

Exposure Assumptions (per day)	Risk Levels and Corresponding Draft Criteria			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish.	0	0.020 µg/l	0.20 µg/l	2.0 µg/l
Consumption of fish and shellfish only.	0	0.040 µg/l	0.40 µg/l	4.0 µg/l

The present American Governmental Conference on Industrial Hygiene (AGCIH, 1977) threshold limit value (TLV) is 670 mg/m^3.

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B. Aquatic

For tetrachloroethylene, the draft criterion to protect saltwater aquatic life is 79 µg/l as a 24-hour average; the concentration should never exceed 180 µg/l at any time (U.S. EPA, 1979).

For freshwater aquatic life, the draft criterion is 310 µg/l as a 24-hour average; the concentration should never exceed 700 µg/l at any time (U.S. EPA, 1979).

This draft criteria to protect aquatic life is presently being reviewed before final recommendation.

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158-11

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No. 159

Thallium

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

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159-2

THALLIUM

Summary

Thallium is a highly toxic element to many organisms, including humans. Symptoms of acute exposure to thallium include alopecia, ataxia, and tremors, occasionally leading to irreversible coma and death. There is no information available on the mutagenic and carcinogenic properties of thallium. Although thallium has been reported to be teratogenic, the evidence is not convincing. The acceptable daily intake (ADI) of thallium has been determined to be 15.4 mg per day. Thallium can be chronically toxic to fish at concentrations as low as 20 µg/l. Algae are also sensitive, with effects produced at concentrations as low as 100 µg/l.

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THALLIUM

I. INTRODUCTION

This profile is based on the Ambient Water Quality Document for Thallium (U.S. EPA, 1979).

Thallium (Tl; atomic weight 204.37) is a soft, malleable, heavy metal with a silver-white luster (Lee, 1971). Thallium exists in either the monovalent (thallous) or trivalent (thallic) form, the former being the more common and stable and therefore forming more numerous and stable salts (Hampel, 1968). Thallium reacts chemically with moisture in air to form oxides. Thallous oxide is easily oxidized to thallic oxide, a very hygroscopic compound, or reduced to thallium. While thallium itself is relatively insoluble in water (Windholz, 1976), thallium compounds exhibit a wide range of solubilities.

Current production and use of thallium and its compounds approximated 680 kg in 1976 (U.S. Dept. Interior, 1977). Industrial uses of thallium include the manufacture of alloys, electronic devices, and special glass. Many thallium-containing catalysts have been patented for industrial organic reactions (Zitko, 1975).

II. EXPOSURE

There is little information on the extent of thallium contamination of water. In a single study by Greathouse (1978) evaluating drinking water from 3,834 households randomly selected from 35 geographic areas, thallium was detectable in only 0.68 percent of the samples (detection limit was 0.3 ppb), with the average concentration at detection of 0.89

ppb. Assuming a water consumption of 2 liters per day for the average adult, over 99 percent of adults would consume < 1 µg per day. The only study pertaining to natural water measured the thallium content of run-offs from mining and smelting operations involving copper, gold, zinc, and cadmium with which thallium is associated in trace quantities (U.S. EPA, 1978). The highest concentrations reported were 30 ppb in slag run-off near Kellog, Idaho and 21 ppb in the Colorado River below drainage from a copper mine.

Ingestion of thallium from food is mainly due to the consumption of vegetables. Little data is available, although Geilmann, et al. (1960) found an average of 68.2 ppb dry weight thallium in four vegetables analyzed. This may be high due to the small sample size. Breads contain 0.75 ppb dry weight thallium, and the thallium content of meats has not been adequately determined. The EPA (1979) estimated the weighted average bioconcentration factor for thallium to be 61 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on measured steady-state bioconcentration studies in bluegill. A daily intake from food has been calculated at 3.8 µg/day. However, due to the sparse data, this is probably not an accurate estimate.

The contribution of thallium in air to exposure is, in most instances, small. However, thallium is a contaminant in flyash, and in a worst case situation in the vicinity of a coal-fired plant, daily absorption could be as high as 4.9 µg (Carson and Smith, 1977). Due to possible high concentrations in vegetable matter, cigarette smoke may be a signifi-

cant source of thallium, with urinary excretion of thallium in smokers being twice that in non-smokers (Weinig and Zink, 1967).

III. PHARMACOKINETICS

A. Absorption

Gastrointestinal absorption of trace quantities of thallium appears to be almost complete in both man (Barclay, et al. 1953) and rats (Lie, et al. 1960). No information was found in the available literature concerning the deposition and clearance of inhaled thallium aerosols. The skin would not be expected to be a significant route of absorption of thallium; however, systemic poisoning has resulted from ointments containing 3-8 percent thallium acetate applied to the skin (Munch, 1934).

B. Distribution

Thallium is widely distributed in the body in the intracellular space. Active transport of thallium, mediated by Na/K ATPase into erythrocytes has been demonstrated (Gehring and Hammond, 1964; Cavieres and Ellroy, 1974). Other factors besides active transport into cells must be operating, since in both conditions of normal thallium exposure and fatal exposure in man, there is a tendency for thallium to concentrate in the kidneys, colon and hair (Weinig and Zink, 1967; Cavanagh, et al. 1974).

Thallium crosses the placenta freely from the maternal circulation to the fetus. In studies using rats and mice, steady state maternal/fetal ratios of 0.84 and 0.46,

respectively, were obtained (Gibson, et al. 1967); and under non-steady state conditions, wide variations in dosage (0.2-6.4 mg/kg/min) did not alter the distribution from mother to fetus (Gibson and Becker, 1970). Richeson (1958) cites one report in which thallium was found in the tissue of a baby whose mother had taken 1.2 g thallium at term.

C. Metabolism

Pertinent information could not be located in the available literature.

D. Excretion

Human excretion of thallium has been estimated from two studies, one involving a tracer dose of 204 Tl given to a middle-age woman with osteogenic carcinoma metastatic to the lungs (Barclay, et al. 1953) and the other involving a woman suffering from thallium poisoning (Innis and Moses, 1978). From these two less than ideal studies, total excretion of thallium per day in adults not exposed to unusual sources of thallium is probably as follows:

Excretory route	ug Tl/day
Urine	1.20
Feces	0.06
Hair	0.32
Skin and Sweat	0.06
Total	1.64

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IV. EFFECTS

A. Carcinogenicity and Mutagenicity

Information regarding the carcinogenic and mutagenic potential of thallium could not be located in the available literature.

B. Teratogenicity

There are two reports of the teratogenicity of thallium, one involving chicken embryos (Karnofsky, et al. 1950) and the other rats (Gibson and Becker, 1970). In both cases, overt fetal toxicity due to thallium was noted, making it impossible to distinguish teratogenicity from a more general toxic effect.

C. Other Reproductive Effects

The only known reproductive effect is fetal toxicity in cases of acute poisoning of the mother.

D. Chronic Toxicity

There are few reports of chronic thallium poisoning in man. In one brief report concerning 13 men exposed 3 to 4, months, the signs and symptoms were pains in the legs, weariness, loss of hair, disturbance of sensation, psychic trouble albuminuria and nephritis (Meyer, 1928).

Rats fed thallous acetate in their diet for 105 days experienced no reduction in weight gain at concentrations of 5 and 15 ppm; 30 ppm, however, proved fatal to approximately half the animals (Downs, et al. 1960).

E. Other Relevant Information

Potassium has been shown to markedly enhance the rate of thallium excretion (primarily urinary) in both rats

and dogs (Gehring and Hammond, 1967). Potassium also increased somewhat the acute LD_{50} of thallium. In humans, potassium also increases urinary excretion with accompanying temporary accentuation of the neurological signs and symptoms (Innis and Moses, 1978; Papp, et al. 1969).

V. AQUATIC TOXICITY

A. Acute Toxicity

The bluegill appears to be extremely resistant to thallium under renewal and static test conditions with 96-hour LC_{50} values of 132,000 and 121,000 µg/l, respectivel (U.S. EPA, 1979). The fathead minnow was tested under flow-through conditions with measured concentrations, and the 96-hour LC_{50} value was found to be 860 µg/l (U.S. EPA, 1978 Atlantic salmon, when exposed to thallium for as long as 2,60 hours, experienced 40 and 70 percent mortality at approximately 20 and 45 µg/l, respectively, with mortality occuring throughout the test (Zitko, et al. 1975). The 48-hour LC_5 for Daphnia magna is 2,180 µg/l (U.S. EPA, 1978).

B. Chronic Toxicity

An embryo-larval test with the fathead minnow indicated adverse effects at the lowest thallium concentration tested of 40 µg/l (U.S. EPA, 1978). No chronic data are available for freshwater invertebrate species, and no chronic effects of thallium on saltwater organisms have been reported (U.S. EPA, 1979).

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C. Plant Effects

There is a 40 percent inhibition of oxygen evolution by the alga, Chlamydomonas reinhardi, exposed to a concentration of 40,800 µg/l (Overnell, 1975). The 96-hour EC_{50} values for chlorophyll a inhibition and cell number are 110 and 100 µg/l, respectively.

D. Residues

The bluegill bioconcentrated thallium 34 times (whole body), and the Atlantic salmon bioconcentrated this heavy metal 130 times above that of the ambient water (Zitko, et al. 1975; U.S. EPA, 1978).

VI. EXISTING GUIDELINES

A. Human

The American Conference of Governmental Industrial Hygienists (ACGIH, 1971) and the Occupational Safety and Health Administration (OSHA) adopted a threshold limit value of 0.1 mg/m^3 for thallium. The acceptable daily intake (ADI) of thallium has been calculated to be 15.4 mg per day. The U.S. EPA (1979) draft water criterion document for thallium recommends a criterion of 4 µg/l for the protection of human health.

B. Aquatic

A criterion for the protection of aquatic species from excess thallium exposure has not been derived.

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LB43-01

No. 160

Toluene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OCTOBER 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

TOLUENE

Summary

The available studies that describe the carcinogenic or mutagenic potential of toluene are inadequate for drawing any conclusions about its carcinogenicity. There is suggestive evidence, based on skin painting experiments in mice, that toluene has a weak promoting effect on DMBA-initiated skin carcinogenesis. Three studies in rats indicate that toluene damages chromosomes in bone marrow cells. Toluene-exposed workers showed an increase (not statistically significant) of chromosome breaks in peripheral lymphocytes. Some neuromuscular deficiencies have been reported in women exposed chronically to toluene in the workplace. Subacute and chronic studies on experimental animals have failed to show evidence of severe cumulative toxicity. Acute exposure to high levels of toluene causes CNS depression. The U.S. EPA (1979) has calculated an ADI of 29.5 mg for toluene.

Toluene is acutely toxic to freshwater fish at concentrations of 6,940 to 32,400 ug/l and to marine fish at concentrations from 4,470 to 12,000 ug/l. A single chronic value of 2,166 ug/l has been reported for marine fish. Aquatic plants appear to be resistant to the action ot toluene with effective concentrations ranging from 8,000 to 433,000 ug/l.

I. INTRODUCTION

This profile is based primarily on the Ambient Water Quality Criteria Document for Toluene (U.S. EPA, 1979) and to a lesser extent on Criteria for a Recommended Standard: Occupational Exposure to Toluene (NIOSH, 1973) and its update (NIOSH, 1977).

Toluene ($C_6H_5CH_3$; molecular weight 92.13) is a clear, colorless, noncorrosive liquid with a sweet pungent odor. It has the following physical and chemical properties (Kirk and Othmer, 1963; Sutton and Calder, 1975; Shell and Ettre, 1971; Weast, et al. 1971):

Boiling Point	110.6°C
Freezing Point	-94.9°C
Flash Point	6-10°C
Vapor Pressure	28 mm Hg at 25°C
Solubility	Water: 534.8 $\pm$ 4.9 mg/l in fresh water and 379.3 + 2.8 mg/l in seawater. Miscible with alcohol, chloroform, ether, acetone, glacial acetic acid, carbon disulfate and other organic solvents.
Production	7.3×10^3 tons/year (USITC, 1977)

Approximately 85 percent of the toluene produced is converted into benzene and other chemicals. The remainder is used as a solvent and as a gasoline additive (NIOSH, 1973).

Little is known about the transport and persistence of toluene in the environment. Toluene is volatile and can evaporate into the atmosphere from bodies of water (MacKay and Wolkoff, 1973). In the atmosphere, toluene is photochemically degraded to benzaldehyde and traces of peroxybenzoyl nitrate. Toluene can re-enter the hydrosphere in rain (Walker, 1976).

II. EXPOSURE

A. Water

No estimates of average daily uptake of toluene from water, food, and air are available. In nationwide surveys of organic chemicals in the drinking water of representative U.S. communities, toluene was found to contaminate 1 raw and 11 finished water supplies out of the 133 water supplies surveyed (U.S. EPA, 1975a; 1975b; 1977). Quantitative analyses of five of the above finished waters revealed levels of toluene ranging from 0.1 ug/l to 19 ug/l. Benzaldehyde and benzoic acid, metabolites of toluene, were also detected. Benzaldehyde was found in the water of five cities, and in two of the cities was measured at levels of 0.1 and 0.5 ug/l. Benzoic acid at 15 ug/l was found in the water of another city.

B. Food

Little data on levels of toluene in food are available. Toluene was detected in sea water and fish obtained near petroleum and petrochemical plants in Japan (Ogata and Miyake, 1973). The muscle of one representative fish contained five ug toluene/g of tissue. Benzaldehyde, a metabolite of toluene, occurs naturally in some foods and is intentionally added to others as a flavoring agent. Benzoic acid, another metabolite of toluene, is added to some foods as a preservative.

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for toluene to be 20 for the edible portions of fish and shellfish consumed by Americans. This estimate is based

on the octanol/water partition coefficient of toluene and on estimates of fish and shellfish consumption.

C. Inhalation

Toluene has been detected in urban air at concentrations many times lower than vapor levels considered to be potentially harmful in occupational settings. An average level of 37 ppb and a maximum level of 129 ppb were measured in the air of Los Angeles (Lonneman, et al. 1968). Comparable levels were found in the air of Toronto, Canada (Pilar and Graydon, 1973), and the air of Zurich, Switzerland (Grob and Grob, 1971). In these latter studies, atmospheric toluene in urban areas appeared to arise primarily from motor vehicle emissions.

III. PHARMACOKINETICS

A. Absorption

No reports are available on oral administration of toluene to humans (U.S. EPA, 1979). Toluene concentrations in arterial blood of persons continuously inhaling toluene vapors appeared to approach equilibrium after 20 to 30 minutes, at which time blood levels were about 1 ug/ml in persons inhaling 100 ppm, and 2 ug/ml in persons inhaling 200 ppm toluene (Astrand, et al. 1972). Systemic uptake of toluene was doubled by exercise, due primarily to increased ventilation rate (Astrand, et al. 1972). This increased uptake of toluene upon exercise was also noted by Carlsson and Lindqvist (1977), who in addition noted that obese persons retain more toluene than thin ones. In their study, the average uptake of toluene vapor during exercise was approximately 49 percent for obese subjects

versus 37 percent for thin subjects. The rate of percutaneous toluene absorption in humans was reported to be 14 to 23 mg/cm^2/hour (Dutkiewicz and Tyras, 1968).

Rats absorbed toluene much more rapidly and developed substantially higher peak blood and tissue toluene concentrations when toluene was administered to the lungs, rather than to the gastrointestinal tract (Pyykko, et al. 1977). Toluene absorption through the skin of experimental animals occurred to a considerably lesser degree than through the lungs or gut (Wahlberg, 1976).

B. Distribution

Toluene is rapidly taken up from the blood into body tissues according to their lipid content and blood perfusion (U.S. EPA, 1979). Partition coefficients (tissue:blood) for toluene in homogenates of rabbit tissues have been determined. The partition coefficient for adipose tissue was 50 times greater, the coefficient for bone marrow was approximately 15 times greater, and those for brain and liver were roughly 2 times greater than the partition coefficients for lung, kidney, heart, and muscle (Sato, et al. 1974). Saturation of liver and brain tissue of mice was not reached even after 3 hours of inhalation of concentrations as high as 4000 ppm toluene (Bruckner and Peterson, 1976).

C. Metabolism

In humans and experimental animals, toluene is thought to be enzymatically converted by the mixed function oxidase (MFO) system to benzyl alcohol, which is subsequently oxidized to benzaldehyde and benzoic acid. Benzoic acid is then conjugated with

glycine to form hippuric acid (U.S. EPA, 1979). There has also been a report, however, of glucuronide conjugation of benzoic acid in rabbits given large doses (Bray, et al. 1951). Toluene toxicity is diminished in rats by MFO inducers (Ikeda and Ohtsuji, 1971) and enhanced by MFO inhibitors (Koga and Ohmiya, 1978), suggesting that metabolism of toluene results in detoxication.

D. Excretion

Toluene is rapidly excreted from the body following inhalation exposure. Most of the estimated absorbed dose of toluene can be accounted for within the first 12 hours as the parent compound in expired air and as hippuric acid in the urine (U.S. EPA, 1979). Elimination rates are slower for women than for men, perhaps because of the larger proportion of fatty tissue in women (U.S. EPA, 1979).

Excretion of toluene in experimental animals is similar to that found in man. In the rat, for example, elimination of toluene occurs more slowly from adipose tissue than from any other (Pyykko, et al. 1977; Carlsson and Lindqvist, 1977), including bone marrow, from which elimination is also relatively slow (U.S. EPA, 1979). Toluene is rapidly lost from the brain, as reflected in rapid recovery from toluene-induced CNS depression (Peterson and Bruckner, 1976; Savolainen, 1978).

IV. EFFECTS

A. Carcinogenicity

The data base on the carcinogenicity of toluene is extremely limited. No inhalation studies have been done. No accounts have been found in the literature in which cancer in

humans has been attributed specifically to toluene. It is difficult to link cancer induction with any single solvent, as persons having occupational exposure to solvents are characterized by considerable job mobility and exposure to a variety of chemicals (U.S. EPA, 1979). Toluene was not demonstrated to be carcinogenic when applied to the skin of mice for one year (Doak, el al. 1976) or throughout a lifetime (Poel, 1963) (since toluene evaporates rapidly, this method is not appropriate). Toluene has not shown carcinogenicity when administered to rats by inhalation at concentrations of up to 300 ppm, 6 hours/day, 5 days/week for as long as 18 months (Gibson, 1979). Frei and Kingsley (1968) reported that toluene has a weak promoting effect on DMBA-initiated skin carcinogenesis in Swiss mice. The major metabolite of toluene, benzoic acid, is not carcinogenic, however, about 1 percent of toluene can be metabolized to o- and p-cresol, which are cancer promoters (Boutwell and Bosch, 1959).

B. Mutagenicity

There is no conclusive evidence that toluene is mutagenic, although it has been reported to cause chromosome damage. For example, the incidence of chromosomal abnormalities in peripheral blood lymphocytes of humans who had been exposed to an average of 200 ppm toluene for as long as 15 years was no greater than in controls (Forni, et al. 1971). However, there have been two reports that toluene induced chromosomal aberrations in the bone marrow cells of rats (Lyapkalo, 1973; Dobrokhotov and Enikeev, 1977), and typographers exposed to toluene have a slightly increased frequency

of chromosome breaks as compared to controls (Funes-Cravioto et al., 1977). Toluene has not been tested in bacterial screening systems (Dean, 1978).

C. Teratogenicity

Although toluene should readily pass the placenta, no reports of teratogenic effects in humans are linked to toluene exposure (U.S. EPA, 1979). Toluene is teratogenic and embryotoxic in mice (Nawrot and Staples, 1979). It was shown to be teratogenic at 1.0 mg/kg, embryolethal at 0.3 ml/kg, and decreased fetal weight occurred at 0.5 ml/kg. There was no maternal toxicity at any dose level on days 6-15, but maternal weight gain was noted for doses given on days 12-15.

D. Other Reproductive Effects

Women occupationally exposed to multiple solvents including toluene through the use of varnishes had a relatively high incidence of menstrual disorders. Their offspring were said to experience more frequent fetal asphyxia, to be more underweight, and not to nurse as well as "normal" infants (Syrovadko, 1977). Dysmenorrhea was a frequent subjective complaint of female shoemakers chronically exposed to 60-100 ppm toluene (Matsushita, et al, 1975). In a single study, some retardation of body weight and skeletal growth were seen in fetuses of rats exposed continuously to 399 ppm toluene on days 1 to 8 of gestation; inhalation of lower levels of toluene had no effect (Hudak and Ungvary, 1978).

E. Chronic Toxicity

The toxicity of toluene was recently reviewed (Lohr and Stokholm, 1979). Its major toxic effects are on the central nervous system, causing depression, headaches, confusion, dizziness, insomnia and (at high exposure levels) death.

A study of 38 female shoemakers exposed chronically to solvents including toluene at 60 to 100 ppm for about three years revealed abnormal tendon reflexes, reduced grasping power, and decreased finger agility when compared to controls (Matsushita, et al., 1975). Reports reviewed by the National Institute for Occupational Safety and Health (1973) have failed to demonstrate adverse effects on the hematopoietic, hepatic, renal, or other physiologic systems of workers routinely inhaling approximately 100 ppm toluene. Chronic exposure may also lead to disturbances in the immune system, dermatitis, and permanent damage to the central nervous system (Cohr and Stockholm, 1979; U.S. EPA, 1979).

F. Other Relevant Information

The primary hazard associated with acute exposure to high levels of toluene is excessive CNS depression (U.S. EPA, 1979). Toluene is capable of altering the metabolism and bioactivity of other chemicals which are metabolized by the mixed function oxidase system. For example, simultaneous administration of toluene and trichloroethylene or toluene and benzene to experimental animals resulted in suppression of metabolism of both compounds (Ikeda, 1974; Ikeda, et al., 1972). Another showed marked reduction in the concentration of benzene metabolites in various tissues, including

bone marrow, after simultaneous administration of toluene, and data that suggested that toluene might protect against benzene myelotoxicity (Andrews, et al., 1977).

V. AQUATIC TOXICITY

A. Acute Toxicity

For freshwater fish, 96-hour static LC_{50} values ranged from 12,700 ug/l for the bluegill (Lepomis macrochirus) to 59,300 ug/l for the guppy (Poecilia reticulatus) (U.S. EPA, 1978; Pickering and Henderson, 1966). Only a single 48-hour LC_{50} value for Daphnia magna of 313,000 ug/l has been obtained for toluene. In marine fish, two 96-hour static LC_{50} values of 6,300 and 10,000-50,000 ug/l were obtained for striped bass (Morone saxatilis) and coho salmon Oncorhynchus kisutch (Benville, et al., 1977). Among four species of marine invertebrates, the bay shrimp (Crago franciscorum) was most sensitive, with a 96-hour static LC_{50} value of 3,700 ug/l (Benville, et al., 1977), while the mysid shrimp Mysidopsis bahia was most resistant, with a 96-hour static LC_{50} value of 56,300 ug/l (U.S. EPA, 1978).

B. Chronic Toxicity

No freshwater chronic data could be found in the available literature. The only marine chronic value reported was 2,166 ug/l for the sheepshead minnow (Cyprinodan variegatus) (U.S. EPA, 1978).

C. Plant Effects

The freshwater algae Chlorella vulgaris and Selenastrum capricornutum were fairly insensitive to the action of toluene: EC_{50} values for cell numbers range from 245,000 ug/l for Chlorella

(Kauss and Hutchinson, 1975) to 433,000 ug/l for Selenastrum (U.S. EPA, 1978). Among five marine algal species tested, Skeletonema costatum was the most sensitive with an adverse effect on growth at 8,000 ug/l (Dunstan, et al., 1975).

D. Residues

No bioconcentration factors are available for toluene in freshwater or marine organisms.

VI. EXISTING GUIDELINES AND STANDARDS

Both the human health and aquatic criteria derived by U.S. EPA (1979), which are summarized below, have not yet gone through the process of public review; therefore, there is a possibility that these criteria may be changed.

A. Human

The NIOSH (1973) recommended standard for exposure to toluene is 100 ppm, determined as a time-weighted average for an 8-hour workday, with a ceiling of 200 ppm.

The U.S. EPA (1979) draft criterion for toluene in ambient water is 12.4 mg/l, corresponding to a calculated acceptable daily intake of 29.5 mg. This criterion is based on chronic toxicological test data for rats (maximum no-effect level of 590 mg/kg, 5 days/wk) and the application of an uncertainty factor of 1000.

B. Aquatic

The draft criterion for the protection of freshwater organisms is 2,300 ug/l, as a 24-hour average, not to exceed 5,200 ug/l; and for marine life the draft criterion is 100 ug/l, as a 24-hour average, not to exceed 230 ug/l.

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No. 161

2,4-Toluenediamine

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

2,4-TOLUENEDIAMINE

Summary

2,4-Toluenediamine produced carcinogenic effects in rats and mice in a long-term National Cancer Institute (NCI) feeding study (50 ppm; 100 ppm). 2,4-Toluenediamine was found to be mutagenic, using mutants of Salmonella typhimurium, hamster embryo cell systems, and Drosophila melanogaster.

2,4-Toluenediamine was also found to be hepatotoxic to rats and mice in the NCI study on carcinogenicity. The compound also hastened the development of chronic renal disease and accelerated animal morbidity. Data concerning the teratogenicity of 2,4-toluenediamine was not found in the available literature. However, a closely related compound, the 2,5-diamino analog, is teratogenic in mice.

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I. INTRODUCTION

2,4-Toluenediamine (molecular weight 122.17) is white solid that melts at 99°C, has a boiling point of 292°C, a density of 1.047 g/cm at 100°C, heat of vaporization of 27.975 kJ/mol, heat of fusion of 19.874, and a specific heat of 2.572 J/g at 150°C (Milligan and Gilbert, 1978). This compound is very soluble in hot benzene, in hot water, and in both alcohol and ether (Weast, 1971). The major use for 2,4-toluenediamine is in the manufacture of 2,4-toluenediisocyanate (TDI), the major raw material for the producton of flexible polyurethane foams and elastomers (Milligan and Gilbert, 1978). The production of 2,4-toluenediamine has increased more than 100 percent since 1966 and was reported in 1976 at 2.05×10^5 tons, with a predicted growth rate of 8-12 percent per year (Milligan and Gilbert, 1978). 2,4-Toluenediamine can also be used in the manufacture of dyes and was an important ingredient in human hair dyes of the permanent, oxidative type until 1971, when its use was restricted after being implicated in the induction of liver carcinomas in rats (Ito, et al. 1969). Using mutants of Salmonella typhimurium, Ames, et al. (1975) found 2,4-toluenediamine to be mutagenic.

II. EXPOSURE

Two potential sources of exposure to 2,4-toluenediamine are in its manufacture and its use as an intermediate in the production of 2,4-toluenediisocyanate. 2,4-Toluenediamine is manufactured by seven U.S. companies at nine U.S. locations (Muller, 1979; Gunn and Cooke, 1976), and most of the corresponding diisocyanate is produced by the same companies at the same locations. Capacity for the latter compound is 3.75×10^5 tons yearly (Muller, 1979). Some additional amounts are consumed in the production of dyes or are exported to manufacturers of 2,4-toluenediisocyanate outside the United States. The amount consumed as a dye intermediate is believed to be

quite small, and the magnitude of the exports of 2,4-toluenediamine is unknown (Gunn and Cooke, 1976). Monitoring data are not available concerning exposure to 2,4-toluenediamine dermally or by water, food, inhalation. Dermal carcinogenicity in mice is discussed below under "Effects" ("Chronic Toxicity").

III. PHARMACOKINETICS

Information on the absorption, distribution, metabolism, and excretion of 2,4-toluenediamine was not found in the available literature.

IV. EFFECTS

A. Carcinogenicity

Carcinoma of the liver with invasion and metastases was observed in rats fed diets containing 0.1 or 0.06 percent 2,4-toluenediamine (Ito, et al. 1969). When the compound was fed at levels of 50 and 100 ppm to inbred barrier-raised F344 rats for 2 years, a statistically significant increase was observed in the incidence of hepatic neoplasia in males, and it induced a significant dose-related positive trend in the incidence of liver neoplasms in both sexes. Hepatocellular changes considered to be associated with neoplasia were increased at a high level of statistical significance in both sexes. The compound also caused statistically significant increases in the incidence of mammary tumors in females, and an increase of mammary tumors in males, although not significant statistically, was believed related to the chemical (Cardy, 1979; Ulland, 1979). 2,4-Toluenediamine was also carcinogenic for female B6C3F1 mice, inducing hepatocellular carcinomas. The incidence of lymphomas in the female mice suggested that these tumors may have been related to administration of the test chemical as well (Ulland, 1979).

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B. Mutagenicity

Fahmy and Fahmy (1977) conducted a comparative assay in Drosophila melangaster for the assessment of the mutagenic efficiency of the hair dye components 2,4-toluenediamine and 4-nitro-o-phenylenediamine relative to benzidine, a human carcinogen which, like 2,4-toluenediamine, is also an aromatic amine. All compounds showed mutagenicity activity. Although activities of the chemicals on the different genetic sites varied between compounds and as a function of cell stage, mutagenic activity did not vary in response to changes in dose. The mutagenicities and selectivities of the test compounds for ribosomal DNA gradually decreased in the order benzidine greater than 2,4-toluenediamine greater than 4-nitro-o-phenylenediamine. For 2,4-toluenediamine a good correlation was found between mutagenicity in the Salmonella/microsome test and morphological transformation in a hamster embryo cell system (Shah, et al. 1977). For mutagenesis, the compound required metabolic activation by a rat liver microsomal enzyme (S9) preparation. In contrast, transformation of hamster cells was induced without activation by external enzymes. In the Ames assay there was no mutagenic activity in the strain TA100, indicating that the product is not a base pair mutagen. The dose response curves obtained with tester strain TA1538 and TA98 show that 2,4-toluenediamine is metabolized by the S9 to a frameshift mutagen (Shah, et al. 1977). In a study of the mutagenic effect of 2,4-toluenediamine in mice, Soares and Lock (1978) found no significant increase in dominant lethal mutations (seven weeks post-treatment) on males.

C. Teratogenicity

Data concerning the teratogenic effects of 2,4-toluenediamine were not found in the available literature. However, 2,5-toluenediamine, a closely related compound which is a hair dye constituent, was found teratogenic in mice (Inouye and Murakami, 1977).

D. Other Reproductive Effects

Information on other reproductive effects was not found in the available literature.

E. Chronic Toxicity

Two reports primarily dealing with carcinogenicity provide information on chronic toxicity. Cardy (1979) found that 2,4-toluenediamine was hepatotoxic when fed at levels of 50 and 100 ppm to inbred, barrier-raised F344 rats for 2 years. The compound also accelerated the development of chronic renal disease in the strain, an effect that contributed to a marked decrease in the survival rate. Giles and Chung (1976), in a chronic toxicity study of 2,4-toluenediamine alone or in combination with selected hair dye complexes, found the compound to be nontoxic and noncarcinogenic to the skin of mice.

F. Acute Toxicity

Lewis and Tatken (1979) summarize the available information:

Oral-human LD_O: 50 mg/kg	Subcutaneous-rat LD_{Lo}: 50 mg/kg
Oral-rat LD_O: 500 mg/kg	Subcutaneous-dog TD_{Lo}: 200 mg/kg
Oral-rat TD_{Lo}: 11 g/kg	Subcutaneous-dog LD_{Lo}: 400 mg/kg

where LD_O--lethal dose to all animals; TD_{Lo}--lowest toxic dose (other than inhalation); LD_{Lo}--the lowest published lethal dose (other than LD_{50}) introduced by any other route than inhalation.

G. Other Relevant Information

Except as reported above, no additional information was found on the effects of 2,4-toluenediamine.

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V. AQUATIC TOXICITY

A. Acute Toxicity, Chronic Toxicity, Plant Effects, and Other Relevant Information.

No information was found in the available literature on acute toxicity, chronic toxicity, plant effects, and other relevant information.

B. Residues

Veith, et al. (1979), in a method of estimating the bioconcentration factor of organic chemicals in fathead minnows (Pimephales promelas), report a log biocentration factor of 1.96 and log n-octanol/water partition coefficient of 3.16* for the fathead minnow in 32 days' exposure. A structure-activity correlation between the bioconcentration factor (BCF) and the n-octanol/water partition coefficient (P) is expressed by the equation—log BCF = 0.85 log P-70. According to the authors, this permits the estimation of the bioconcentration factor of chemicals to within 60 percent before laboratory testing.

VI. EXISTING GUIDELINES AND STANDARDS

No existing guidelines or standards were found in the available literature.

*Under the same conditions the log n-octanol/water partition coefficient for heptachlor was 5.44; for hexachlorobenzene, 5.23; for mirex, 6.89; and for dipheylamine, 3.42.

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No. 162

Toluene Diisocyanate

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OCTOBER 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

TOLUENE DIISOCYANATE

Summary

Toluene diisocyanate (TDI) is used in the manufacture of polyurethane foam. TDI is formed through the reaction of 2,4-toluenediamine with phosgene. The TDI is then reacted with di- and poly-functional hydroxy compounds to form polyurethane foam.

TDI is readily reactive in water, forming carbon dioxide and polyurea derivatives. Environmental occurence of TDI is unlikely due to its high reactivity with hydroxy compounds and peroxy radicals.

Information on the teratogenicity of toluene diisocyanate was not found in the available literature. TDI after being tested by the National Cancer Institute for carcinogenicity using a standard bioassay protocol, was found not be carcinogenic. Additionally, toluene diisocyanate did not show mutagenic activity on testing of Salmonell typhimurium strains with and without a mammalian liver microsome activating system.

Extensive toxicologic data exists for TDI, primarily from occupational exposure studies. TDI produces respiratory effects, including mucous membrane irritation, bronchoconstriction, coughing, and wheezing. Exposure to high concentrations can result in pulmonary edema or death.

The effects of chronic, low-level exposure to TDI vary. Decreased lung function has been reported from inhalation of 0.003 ppm TDI, but other investigators have not seen these respiratory effects from inhalation of 0.02 ppm TDI. Hypersensitivity to TDI has also been observed from occupational respiratory exposure. Immunologic and pharmacologic reactions have been proposed as the mechanism of action of TDI.

Other reported effects include memory loss, psychological disturbances, and skin irritation. Uncertainty exists regarding the frequency of these effects in those occupationally exposed. Maintaining exposure below 0.005 ppm has proven effective in protecting health of unsensitized workers. Where an individual has previously been sensitized, a no-threshold effect is indicated upon subsequent exposure to TDI.

TOLUENE DIISOCYANTE

Environmental Fate

Toluene diisocyanate (TDI) readily reacts with hydroxy compounds. Its atmospheric half-life is approximately three days (Brown, et al. 1975). TDI readily hydrolyzes in neutral aqueous media, or more rapidly under acidic or basic conditions, to give unstable carbamic acids (Tennant, 1979). These acids tend to lose carbon dioxide, giving the corresponding amine which, in turn, reacts with the starting isocyanate to produce a urea derivative. This reaction produces a concurrent decrease in pH (Curtis, et al. 1979). TDI readily hydrolyzes in water, and has a half-life of 0.5 seconds to 3 days, depending on pH (Brown, et al., 1975). As temperature increases the reaction becomes more vigorous (Tennant, 1979).

Brown, et al. (1975) concluded that because of the short lifetime of toluene diisocyanate in water, its occurrence in this medium is unlikely.

Toluene diisocyanate is persistent in the atmosphere. Under atmospheric conditions reaction with ozone leads to an atmospheric half-life of 3,981 days. The reaction of TDI with peroxyradical groups has an environmental half-life of approximately 7.94×10^5 days in the water phase.

I. INTRODUCTION

This profile is based upon relevant literature identified through bibliographic searches in TOXLINE and Chemical Abstracts, and through manual searches. The National Institute for Occupational Sefety and Health (NIOSH) has published a criteria document for diisocyanates (NIOSH, 1978). This report represents a comprehensive review of the available toxicologic literature on toluene diisocyanate (TDI) and was the source for much of the data described below.

Toluene diisocyanate is also reported as 2,4-diisocyanate-1-methylbenzene, tolylene diisocyanate, methylphenylene isocyanate, diisocyanotoluene, and stilbene diisocyanate. The compound is a colorless-to-pale yellow liquid. The chemical formula is $C_9H_6N_2O_2$. Physical properties of TDI are as follows: molecular weight, 174.16; melting point, 20 to 22°C; boiling point, 251°C; vapor pressure, 0.05 mm Hg at 25°C; and specific gravity, 1.22 at 25°C (NIOSH, 1978). TDI is soluble aromatic hydrocarbons, nitrobenzene, acetone, ethers, and esters.

The most common method of synthesizing toluene diisocyanate is through the primary reaction of diaminotoluene with phosgene. Toluene diisocyanate is then reacted with di- and poly-functional hydroxy compounds to form poly-urethane foams, coatings, elastomers, and spandex fibers (NIOSH, 1978).

Toluene diisocyanate production in the U.S. was 605 million pounds (Predicasts, Inc., 1980) in 1978, with an estimated 6.4 percent annual growth in production. Production capacity amounted to 775 million pounds per year in 1978.

II. EXPOSURE

Respiratory and dermal exposure to toluene diisocyanate has been well documented in occupation environments (NIOSH, 1978). Sources of occupational exposures include production processes of basic TDI manufacture, production of polyurethane foam, and accidental releases or spills in product synthesis, transportation, use, or disposal.

Non-occupational exposure to TDI through ingestion of contaminated food or water is unlikely since TDI released to the environment would readily react with other compounds, forming stable polyurea end products. For example, Curtis, et al. (1979) conducted acute aquatic toxicity studies of TDI and reported the immediate reaction of TDI with water resulting in the production of carbon dioxide and a polyurethane foam-like solid. Human exposures would most likely occur to these polyurea compounds and not TDI. Accidental releases and spills may result in respiratory TDI exposure of persons in the immediate vicinity. Dermal exposure may also occur in persons coming in direct contact with the compound.

III. PHARMACOKINETICS

Information on the abosrption, distribution, metabolism, and excretion of TDI was not identified in the available literature. NIOSH (1978), in describing the sensitization phenomenon of TDI exposure, hypothesized that this response may be the result of TDI reaction with *in vivo* hydroxyl, amino, sulfhydryl, or similar compounds which form a hapten complex with TDI. This complex is believed to be responsible for the sensitization of individuals to TDI.

IV. EFFECTS

A. Carcinogenicity

TDI did not show carcinogenic activity after being tested by NCI using a standard bioassay protocol.

B. Mutagenicity

Toluene diisocyanate did not show mutagenic activity on testing Salmonella typhimurium strains with or without a mammalian liver microsome activating system (NIOSH, 1978).

C. Teratogenicity and Other Reproductive Effects

Information on teratogenic or other reproductive effects of toluene diisocyanate was not found in the available literature.

D. Chronic Effects

Inhalation of toluene diisocyanate represents the primary route of exposure and produces chronic effects; the mechanism of the chronic respiratory changes is uncertain.

Toluene diisocyanate induces a hypersensitive reaction in specific individuals. Predisposing factors may include both environmental and endogenous host factors (Adkinson, 1977). Intensity and duration of exposure are important in eliciting a hypersensitive reaction. Genetic factors controlling immune responsiveness, metabolic aberration were suggested as factors influencing the allergic reaction (Adkinson, 1977). However, Butcher, et al. (1976) found no pattern of prior hay fever or asthama, or of skin sensitization in clinically sensitized individuals.

Exposure to high concentrations has caused respiratory sensitization in workers (Walworth and Virchow, 1959; Bruckner, et al. 1968). These sensitization reactions were described earlier. The sensitization can progress to a condition resembling chronic bronchitis and pulmonary edema. Individuals sensitized to TDI present an asthmatic reaction upon reexposure to very low concentrations of TDI. Butcher, et al. (1979) described four specific types of responses in hypersensitive workers: (1) immediate; (2) late; (3) dual; and (4) dose-related. The responses were measured as percent change in one-second Forced Expiratory Volume (FEV_1) over time. Immediate response occurred within one hour of exposure, whereas late response exhibited a gradual decline in FEV_1 over five hours. The dual response elicited an early response within one hour and a late response after eight hours. The dose-related response was exhibited at 0.01 ppm, whereas exposure to 0.005 ppm did not show a significant decrease in FEV_1. The author suggested a pharmacologic basis for the hypersensitivity, but noted that an allergic mechanism could not be ruled out.

Porter, et al. (1975) reported sensitization correlated with the frequency and severity of significant exposures greater than 0.05 ppm. Once sensitized, an individual exposed to very low concentrations of TDI will produce asthmatic reactions upon subsequent TDI exposure.

Wegman (1977) reported decrements in FEV_1 in both sensitized and unsensitized workers. However, Adams (1975) and Butcher, et al. (1977) did not show decreased FEV_1 after occupational exposures of 11 and 2.5 years, respectively. TDI concentrations were 0.02 ppm and below, with occasional excursions above this level. Consequently, the National Institute for Occupational Safety and Health (NIOSH) recommended an eight hour time-weighted average limit of 5 ppb, noting that the above studies and others had not reported significant effects on lung function at concentrations of 14-50 ug/m^3 (2.0-7.0 ppb).

Some authors have reported skin sensitization in persons occupationally exposed to TDI (Nava, et al. 1975; Karol, et al. 1978), but other investigators have not observed such skin sensitization reactions (Munn, 1960; Bruckner, et al. 1968).

Other chronic effects from TDI exposure include neurologic effects, eye irritation, and psychological symptoms. Le Quesne, et al. (1976) reported memory loss lasting 4 years in workers exposed to massive concentrations of TDI while fighting a fire at a polyurethane foam factory.

F. Acute Effects

Inhalation of TDI is the primary route of exposure which has demonstrated acute effects. Several authors have reported daily and cumulative decreases in lung function following respiratory exposure to TDI. Investigations of

acute effects from TDI exposure have produced contradictory results. Peters, et al. (1968) reported significant decreases in lung function upon exposure to 0.1-3.0 ppb, whereas Adams (1975) noted no significant decrease in lung function at 20 ppb.

Occupational exposure to high concentrations of TDI causes direct irritation of the respiratory tract (Walworth and Virchow, 1959; Maxon, 1964; Axford, et al. 1976; Gandevia, 1963).

Eye, nose, and throat irritation was observed upon atmospheric exposures to 500 ppb (Henschler, 1962). Nausea, vomiting, and abdominal pain may also occur (Key, et al. 1977). Dermal contact with liquid TDI may produce redness, swelling, and blistering. Contact with eyes may produce severe irritation and permanent damage. Ingestion of TDI may cause burns of the mouth and stomach (Key, et al. 1977).

Lewis and Tatken (1979) reported an inhalation LC_{50} for rats of 600 ppm following a 6-hour exposure; and an inhalation LC_{50} for mice of 10 ppm following a 4-hour exposure.

V. AQUATIC TOXICITY

A. Acute Toxicity

Curtis, et al. (1979) reported a 96-hour LC_{50} of 164.5 mg/1 in the fathead minnow (Pimephales promelas). No significant mortality was noted in grass shrimp (Palaemonetes pugio) exposed to 508.3 mg/1. The authors noted that TDI

reacted with water of dilution, and concluded that TDI was toxic to the fathead minnow in the unreacted form only, as evidenced by all mortalities occurring during the first 12 hours of the test. However, the authors did note that a concurrent decrease in pH was observed as a result of carbon dioxide formation from TDI reactivity. Lewis and Tatken (1979) reported an aquatic toxicity rating, TLm_{96} (equivalent to a 96-hour LC_{50}) of 1.0-10.0 ppm. Thus TDI has moderate acute toxicity to aquatic organisms.

B. Chronic Toxicity, Plant Effects, and Residues

Pertinent data could not be located in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

The Occupational Safety and Health Administration (OSHA) regulates TDI by specifying a PEL for airborne TDI of 0.14 mg/ m^3 (40 CFR 1910.1000) as a 15-minute exposure.

The American Conference of Governmental Industrial Hygienists (1979) has recommended a threshold limit value-time weighted average for toluene diisocyanate of 5 ppb (0.04 mg/m^3). NIOSH (1978) recommended a time-weighted-average limit for airborne toluene diisocyanate of 5 ppb, with a ceiling value of 20 ppb. NIOSH (1978) also reported occupational exposure limits for TDI in numerous countries. These limits ranged from 0.07 to 0.5 mg/m^3.

TOLUENE DIISOCYANATE

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No. 163

Toxaphene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated toxaphene and has found sufficient evidence to indicate that this compound is carcinogenic.

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TOXAPHENE

SUMMARY

Toxaphene is a mixture of polychlorinated camphenes. It is obtained from camphene by photochemical chlorination, which produces a heterogeneous mixture of chemicals (177) containing 67 to 69 percent chlorine. Toxaphene has not produced teratogenic effects in laboratory animals, but has been found to be mutagenic in two strains of Salmonella typhimurium with metabolic activation. A National Cancer Institute (NCI) 1979 study found that toxaphene significantly increased the incidences of hepatocellular carcinomas in mice.

The insecticide toxaphene has been demonstrated to be a potent toxin to a variety of aquatic life. For both freshwater and marine fish species, acute toxicity values of 0.8 to 28 µg/l were reported. Marine invertebrate species displayed considerable interspecies variation, with LC_{50} values ranging from 0.08 to 2,700 µg/l.

TOXAPHENE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria document for Toxaphene (U.S. EPA, 1979).

Toxaphene is a commercially produced, broad spectrum, chlorinated hydrocarbon consisting primarily of chlorinated camphene and related compounds and isomers. It is currently the most heavily used insecticide in the U.S., with an annual production rate exceeding 50 x 10^3 tons (U.S. EPA, 1979).

On May 25, 1977, because of its carcinogenic effects, aquatic toxicity, and high bioconcentration factor, the U.S. EPA issued a notice of rebuttable presumption against registration and continued registration of pesticide products containing toxaphene.

Toxaphene is an amber, waxy solid with a mild terpene odor and an average molecular weight of 414. Its physical properties include: melting point of 65-90°C; vapor pressure, 0.17-0.40 mm Hg at 25°C; solubility in water, 0.4-3.0 mg/l; and is soluble in relatively non-polar solvents, with an octanol/water partition coefficient of 825 (U.S EPA, 1979).

The commercial product is relatively stable but may dehydrochlorinate upon prolonged exposure to sunlight, alkali, or temperatures above 120°C (Metcalf, 1966; Brooks, 1974). In natural water systems, toxaphene tends to be absorbed by the particulates present or to be taken up by living organisms and bioconcentrated. Thus, it is seldom found as a soluble component in receiving waters but can persist

in sediments or remain absorbed on suspended solids for prolonged periods (U.S. EPA, 1979).

II. EXPOSURE

A. Water

Toxaphene has been monitored in the U.S. since 1959. Although it has been detected at several locations, it is not found in all waters (U.S. EPA, 1979). Seven routine monitoring studies of U.S. surface water prior to 1975 did not detect toxaphene (U.S. EPA, 1979).

Nicholson, et al. (1964, 1966) detected toxaphene in the drinking water obtained from Alabama at levels ranging from 0.01-0.1 µg/l. A survey of commercial drinking water samples by the U.S. EPA (1976a) during 1975 and 1976 found no detectable levels of toxaphene (limit of detection 0.05 µg/l).

Toxaphene has been detected in water around areas where it is applied to crops as an insecticide. For example, it has been detected in surface waters in California at levels ranging from 0.02 to 7.9 µg/l, and in drainage effluents at levels of 0.130 to 0.950 µg/l (Johnston, et al. 1967; Bailey and Hammon, 1967). Several studies of an agricultural watershed in Alabama found that treatment of drinking water did not reduce toxaphene concentrations (U.S. EPA, 1979).

Toxaphene has been detected in the sediment samples of various waters even when it is not found in samples of the surface waters (Mattraw, 1975). Concentrations as high as 2.46 µg/l have been found in sediments (U.S. EPA, 1979).

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Sediment samples at three locations downstream of a plant producing toxaphene had a maximum residue level of 15 µg/l toxaphene before dredging (Reimold and Durant, 1972).

B. Food

The best available estimate of dietary intake of toxaphene is 0.021 µg/kg/day, based on the U.S. Food and Drug Administration basket survey between 1964 and 1970 (Duggan and Corneliussen, 1972). Based on recent market basket surveys indicating a decrease in the incidence of toxaphene contamination, a stable incidence of toxaphene in raw meat since 1969, and a two-fold increase in the incidence of toxaphene in unprocessed food samples between 1972 and 1976, the U.S. EPA (1979) estimates the current dietary intake to be 0.042 µg/kg/day.

The U.S. EPA (1979) has estimated the weighted average bioconcentration factor for toxaphene to be 18,000 for the edible portions of fish and shellfish consumed by Americans. This estimate was based on the measured steady-state bioconcentration studies in five species of fish and shellfish.

C. Inhalation

The highest toxaphene residues in air have been found in areas where toxaphene is applied for agricultural purposes (especially cotton production in the Southern U.S.) (U.S. EPA, 1979). Studies indicate that airborne residues are highest during cotton growing season and decrease to low levels after harvesting, but spring tilling releases

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soil residues to the air. Concentrations ranging from 0 to 2520 ng/m^3 have been measured in southern agricultural areas (Arthur, et al. 1976; Stanley, et al. 1971.) Mean monthly concentrations have been measured as high as 167 ng/m^3 (Arthur, et al. 1976).

Toxaphene has also been monitored in the atmosphere over the east coast near Bermuda and the open ocean (Bidleman and Olney, 1975). The mean concentrations were 0.79 and 0.53 ng/m^3, respectively. Using the maximum mean monthly concentration of 167 ng/m^3 (Arthur, et al. 1976), the average daily dose of toxaphene from air is approximately 0.057 µg/kg (U.S. EPA, 1979). This amount would reflect intake at a high toxaphene use area, whereas a more conservative value using a concentration of 0.53 ng/m^3 monitored over open ocean (Bidleman and Olney, 1975) would be an average daily intake of 0.18 ng/kg of toxaphene from air (U.S. EPA, 1979).

D. Dermal

Toxicity studies with laboratory animals indicate that toxaphene can be absorbed across the skin in toxic amounts by humans (U.S. EPA, 1979). Incidence of dermal absorption of toxaphene by humans is restricted to occupational or accidental exposure.

III. PHARMACOKINETICS

A. Absorption

The recently completed U.S. EPA (1978) study suggests that inhalation exposures to toxaphene do not result in sufficient absorption by humans to cause quantifiable levels in the blood.

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Animal studies show absorption of toxaphene across the alimentary tract, skin, and respiratory tract, as indicated by adverse effects elicited by oral, dermal, and inhalation exposures (U.S. EPA, 1979). The vehicle and mode of administration, as well as individual differences, affect the rate of absorption of toxaphene. The ratio of oral LD_{50} to dermal LD_{50} (in comparable lipophilic solvents) is about 0.1 (Lackey, 1949a,b; Conley, 1952; U.S. EPA, 1979).

B. Distribution

Toxaphene is readily distributed throughout the body, with highest residues found in fat tissue. Three hours after single intubations of Cl-36 labelled toxaphene, rats had detectable levels of Cl-36 activity in all tissues examined (kidney, muscle, fat, testes, brain, blood, liver, intestines, esophagus, spleen, and stomach), with the highest levels being found in the stomach and blood (Crowder and Dindal, 1974.) After 9 to 14 days, most of the activity is found in the fat, blood, kidney, liver, and intestines (Crowder and Dindal, 1974; Ohsawa, et al. 1975). The predominance of fat storage had been demonstrated in 12-week feeding studies with rats, and 2-year feeding studies with rats and dogs (Clapp, et al. 1971; Lehman, 1952; Hercules, Inc., undated). In the above studies, toxaphene residues were highest in fat tissues but always remained below the levels administered in the diet, thus suggesting that toxaphene is not biomagnified in terrestrial organisms (U.S. EPA, 1979).

C. Metabolism

Toxaphene undergoes reductive dechlorination, dehydrochlorination, and hydroxylation in mammalian systems (U.S. EPA, 1979). Studies by Crowder and Dindal (1974), Ohsawa, et al. (1975) and Khalifa, et al. (1976) have observed 50 percent dechlorination of toxaphene after administration by intubation to rats, or *in vitro* with rat liver microsomes and NADPH under anaerobic conditions. Toxaphene has been suggested as a substrate for the hepatic microsomal mixed-function oxidases because of type I binding spectra with cytochrome P-450, and NADPH dependence (Kulkarni, et al. 1975; Chandurkar, 1977).

Several investigators have noted that fat residues of toxaphene resemble whole toxaphene, while residues in both the liver and feces are consistently more polar (Pollock, 1978; Saleh, et al. 1977).

D. Excretion

The half-life of C-14 or Cl-36 labelled toxaphene in rats after single oral doses appears to be from one to three days, with most of the excretion occurring via the urine and feces (Crowder and Dindal, 1974; Ohsawa, et al. 1975). Only a small portion of the urine and fecal metabolites is eliminated as glucuronide or sulfate conjugates (Chandurkar, 1977).

A study of the blood levels of toxaphene in an individual consuming contaminated fish (52 µg toxaphene/g fish) revealed levels of 142 ppb, 47 ppb, $<$30 ppb on day 1, day 11, and day 14 of measurement (U.S. EPA, 1978).

IV. EFFECTS

A. Carcinogenicity

The National Cancer Institute (1979) has recently completed a carcinogenicity bioassay of toxaphene. The 80-week feeding study did not follow current NCI standards; only ten animals were used in each matched control group, and matched-fed control groups were not utilized (NCI, 1977). The feeding schedule was as follows: for rats - males, time weighted average (TWA) doses at 556 mg/kg and 1,112 mg/kg, and females, TWA doses at 540 mg/kg and 1,080 mg/kg; and for mice, males and females, TWA doses at 99 mg/kg and 198 mg/kg.

In male rats in the high dose group, a significant increase was noted in the incidence of follicular-cell carcinomas and adenomas of the thyroid. Of the nine thyroid tumors which were found in this group, two were carcinomas. A significant increase of follicular-cell adenomas of the thyroid was also noted in the high-dose group of female rats. No carcinomas of the thyroid were found in this group. In both of these groups, the development of thyroid tumors was dose-related.

In both male and female mice, significant increases were noted in the incidence of hepatocellular carcinomas and in the incidence of hepatocellular carcinomas combined with neoplastic nodules of the liver.

Based on the results of this study, the National Cancer Institute has concluded that "Toxaphene was carcinogenic in male and female B6C3F1 mice, causing increased

incidences of hepatocellular carcinomas. The test results also suggest carcinogenicity of toxaphene for the thyroid of male and female Osborne-Mendel rats" (NCI, 1979).

Litton Bionetics, Inc. (1978) also reported a significant excess of hepatocellular tumors (hepatocellular adenoma plus hepatocellular carcinoma) in male mice fed dietary levels of 50 ppm toxaphene.

B. Mutagenicity

The mutagenicity of toxaphene has been tested in bacterial systems using Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98, and TA100 (Hill, 1977). Positive test results were obtained for strains TA98 (frameshift mutation) and TA100 (base pair substitution) only in tests without metabolic activation. All other tests were negative. A "high temperature" toxaphene has elicited positive dose response increases in strains TA98 and TA100 only with metabolic activation. In other studies, toxaphene and toxaphene subfractions have been found to be mutagenic to strain TA100 with or without metabolic activation (Hill, 1977).

A study conducted by the U.S. EPA (1978) found no significant differences in the rates of chromosomal aberrations in leukocytes between groups of workers occupationally exposed to toxaphene and those not exposed.

C. Teratogenicity

Toxaphene did not produce teratogenic effects when administered in the diet of rats, mice, and guinea pigs (U.S. EPA, 1979). Kennedy, et al. (1973) found no indication of teratogenic effects in F3 weanlings of rats

fed toxaphene at levels of 25 mg/kg diet and 100 mg/kg diet. Pregnant rats and mice fed 15 to 35 mg/kg/day of toxaphene produced young with no teratogenic effects as did pregnant guinea pigs fed 15 mg/kg body weight (Chernoff and Carver, 1976; DiPasquale, 1977).

D. Other Reproductive Effects

Adverse effects on fertility, gestation, viability, lactation, or survival indices were not observed in male and female rats fed dietary levels of 25 mg/kg and 100 mg/kg toxaphene (Kennedy, et al. 1973), or in mice fed dietary levels of 25 mg/kg toxaphene (Keplinger, et al. 1970).

E. Chronic Toxicity

Long term exposures to low dietary levels of toxaphene have been investigated in several studies involving rats, dogs, and monkeys (U.S. EPA, 1979). All studies noted some form of liver pathology in rats at dietary levels of 100 mg/kg or above. At 100 mg/kg, cytoplasmic vacuolization was noted by Kennedy, et al. (1973). Increased liver weight with minimal liver cell enlargement was noted in rats at dietary levels of 25 mg/kg (Fitzhugh and Nelson, 1951). The lowest dietary level of toxaphene producing unequivocal liver damage over a two-year feeding period was 20 mg/kg (U.S. EPA, 1979). Only at high concentrations, i.e., 1,000 mg/kg diet, does toxaphene elicit central nervous system effects (Hercules, Inc., undated).

F. Other Relevant Information

Induction of hepatic microsomal mixed-function oxidase (MFO) appears to account for most of the interactions

of toxaphene with other compounds (U.S. EPA, 1979). Pretreatment with known MFO inducers, such as DDT, aldrin, and dieldrin, increases oral LC_{50}'s two to three-fold (Deichman and Keplinger, 1970). Piperonyl butoxide, which inhibits the metabolism of many toxicants by MFO, has been shown to potentiate the toxicity of toxaphene in houseflies (Saleh, et al. 1977).

Keplinger and Deichmann (1967) found that equitoxic combinations of toxaphene with parathion, diazinon, or trithion were less toxic than expected based on the assumption of simple similar action.

Acute human intoxication by toxaphene-lindane mixtures produces signs and symptoms that are not characteristic of toxaphene or lindane poisoning (Pollock, 1958; Masumura, 1975).

V. AQUATIC TOXICITY

A. Acute

Acute toxicity data of toxaphene to freshwater fish are derived from 52 96-hour LC_{50} values for 18 species resulting from 48 static and 4 flow-through assays. Observed LC_{50} values for these species of fish range from 0.8 µg/l for the channel catfish (Ictalurus punctatus) to 28 µg/l for the goldfish, (Carassius auratus) (U.S. EPA, 1979). No single family or species appeared to be dramatically more resistant or sensitive to toxaphene. For freshwater invertebrates, 17 static bioassays on 13 species resulted in reported LC_{50} values of 1.3 µg/l for the stonefly (Claasenia sabulosa) to 178 µg/l for the crayfish (Procambarus simulans) (U.S. EPA, 1978).

For the marine fish, toxicity data were determined from five flow-through and two static assay procedures representing six species. Observed LC_{50} values ranged from 0.5 µg/l for the pinfish (Lagodon rhomboides) to 4.7 µg/l for the threespine stickleback (Gasterosteus aculeatus) (U.S. EPA, 1979). The toxicity of toxaphene to marine invertebrates shows considerable interspecific variation in 31 assays (10 flow-through and 21 static) with reported LC_{50} values ranging from 0.054 µg/l for larval stages of the driftline crab (Sesarma cineseum) to 2,700 µg/l for the blue crab (Callinecten sapilus).

B. Chronic

Chronic life cycle toxicity tests have produced chronic values of 0.037 and 0.059 µg/l for the fathead minnow (Pimephales promelas) and channel catfish (Ictalurus punctatus), respectively (Mayer, et al. 1977). Growth effects were noted in brooktrout chronically exposed to concentrations of 0.038 µg/l. Life cycle tests on freshwater invertebrates have been performed on three species with chronic values of 0.09, 0.18, and 1.8 µg/l reported for Daphnia magna; the scud (Gammarus pseudolimnaeus); and midge larvae (Chironomus plumosus), respectively (Sanders, in press). An embryo-larval test on the marine fish sheepshead minnow (Cyprinodon variegatus) produced a chronic value of 0.83 µg/l (Goodman, et al. 1978). A chronic value of 0.097 µg/l was obtained for the marine mysid shrimp (Mysidopsis bahia) (Nimmo, 1977).

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C. Plant Effects

No data for the effects of toxaphene were found for freshwater species. Effective concentrations for five species of marine plants ranged from 0.15 µg/l for reduced growth in the dinoflagellate (Monochrysis lutheri) to 150 µg/l for lethality in the dinoflagellate (Danaliella euchlora) and no growth of the algae (Protococcus) sp. (U.S. EPA, 1978).

D. Residues

Bioconcentration factors for three species of fish were reported (Mayer, et al. 1975; Mayer, et al. 1977). Brooktrout fry (Salvelinus fontinalis) had the highest factor of 76,000 in 15 days, while yearling brooktrout had the lowest factor of 16,000 in 161 days. In the marine longnose killifish (Fundulas similis), bioconcentrations for a number of different life stages were reported as 29,450 for juveniles, 27,900 for fry, 5,400 for adults, and 1,270 to 3,700 for ova of exposed adults (Schimmel, et al. 1977).

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

The standards for toxaphene in air, water, and food which have been established or recommended by various groups and agencies were set before the results of the NCI bioassay for carcinogenicity were available (U.S. EPA, 1979).

The ACGIH (1977) recommends a time weighted average value of 500 mg/m^3 for the working environment and a tentative short-term exposure limit of 1 mg/m^3. The national interim primary drinking water standard for toxaphene is 5 µg/l (40 FR 11990; U.S. EPA, 1976b, 1976c). The National Academy of Sciences (1977) estimated the acceptable daily intake of toxaphene for man at 1.25 µg/kg and suggested no-adverse-effect levels from water at 8.75 µg/l (assigning 20 percent of the total ADI to water) or 0.44 µg/l (assigning 1 percent of the total ADI to water). Effluent standards for toxaphene manufacturers have been set at 1.5 µg/l for existing facilities and 0.1 µg/l for new facilities (U.S. EPA, 1976a). Tolerances established by the U.S. Food and Drug Administration for toxaphene in various agricultural products range from 0.1 mg/kg in sunflower seeds to 7 mg/kg in meat fat (U.S. EPA, 1979).

The U.S. EPA (1979) draft water quality criterion for toxaphene is 0.467 ng/l or 4.7×10^{-4} µg/l. This criterion is based on the NCI (1979) study that reported hepatocellular carcinoma and neoplastic nodules in mice fed toxaphene; the criterion was calculated to keep the lifetime cancer risk below 10^{-5} for humans.

B. Aquatic

A drafted criterion for the protection of freshwater aquatic organisms is 0.007 µg/l for a 24-hour average concentration, not to exceed 0.47 µg/l at any time. For marine aquatic life, the drafted criterion is 0.019 µg/l for a 24-hour average concentration not to exceed 0.12 µg/l at any time (U.S. EPA, 1979).

TOXAPHENE

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SJ-46-01

No. 164

1,1,1-Trichloroethane

(Methyl Chloroform (MC))

• Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

October 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in this report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

1,1,1-TRICHLOROETHANE (MC)

SUMMARY

Results of an NCI carcinogenesis bioassay of MC was inconclusive due to experimental problems. NCI and a manufacturer are currently re-evaluating its carcinogenic potential. *In vitro* studies have indicated that MC is slightly mutagenic with or without activation, and can cause mammalian cell transformation. Studies of the teratogenic potential of MC are suggestive; however, more studies are needed to make a conclusive statement. Inhalation exposure of healthy adults to the current PEL for MC (350 ppm) has generally resulted only in untoward psychophysiologic effects. Animal studies, as well as accidental human exposure have shown that MC, at high inhalation concentrations, produces microscopic pathology of liver and kidneys which is much less severe than that produced by carbon tetrachloride or tetrachloroethylene. MC is moderately toxic to aquatic life.

I. INTRODUCTION

The chlorinated ethanes are hydrocarbons in which one or more of the hydrogen atoms of ethane are replaced by chlorine atoms. Water solubility and vapor pressure decrease with increasing chlorination, while density and melting point increase. At room temperature, 1,1,1-trichloroethane (M.W. 133.4) is a liquid with a boiling point 74.1°C, a vapor pressure (20°C) of 100 torr, a melting point of -33°C, a specific gravity of 1.3492, and a low solubility in water (U.S. EPA, 1980a).

The chloroethanes are used as solvents, cleaning and degreasing agents, and in the chemical synthesis of a number of compounds.

The 1976 production of 1,1,1-trichloroethane was: 3×10^3 kkg/year (U.S. EPA,1980a).

The chlorinated ethanes form azeotropes with water (Kirk and Othmer, 1963). All are very soluble in organic solvents (Lange, 1956). Microbial degradation of the chlorinated ethanes has not been demonstrated (U.S. EPA, 1980a).

The reader is referred to the Chlorinated Ethanes Hazard Profile for a more general discussion of chlorinated ethanes (U.S. EPA, 1980b).

II. EXPOSURE

The chloroethanes present in raw and finished waters are due primarily to industrial discharges. Small amounts of the chloroethanes may be formed by chlorination of drinking water

or treatment of sewage. Air levels of chloroethanes are produced by evaporation of these compounds, widely used as degreasing agents and in dry cleaning operations (U.S. EPA, 1980a). Occupational air monitoring studies have indicated 1,1,1-trichloroethane levels ranging from 1.5 to 396 ppm (U.S. EPA, 1980a).

Sources of human exposure to chloroethanes include water, air, ingestion of contaminated foods and fish, and dermal absorption.

Human exposure to MC was estimated from ambient air monitoring data. At 8 cities values of 0.02 to 1.86 ug/kg/day were calculated. At one city, however, where an Mc manufacturing facility is located, 12-86 ug/kg/day was calculated (USEPA 1980), Drinking water showed only traces (0.05-1.0 ppb) of MC, except near a MC producing facility (USEPA, 1980).

An analysis of several foods indicated 1,1,1-trichloroethane was present at levels of 1-10 ug/kg (Walter, et al., 1976). Fish and shellfish have shown levels of 1,1,1-trichloroethane in the nanogram range (Dickson and Riley, 1976).

The U.S. EPA (1980a) has estimated the weighted average bioconcentration factor for 1,1,1-trichloroethane to be 21 for the edible portions of fish and shellfish consumed by Americans. This estimate is based on the measured steadystate bioconcentration studies in bluegills.

III. ATMOSPHERIC FATE AND TRANSPORT

Because of its volatility, its transformation into other potentially harmful atmospheric components, its tropospheric chemical reactivity, and its diffusion into the stratosphere, MC is thought to pose a hazard to human health.

The volatilization of MC from water can be reversible because it is stable in the atmosphere and is transported back to surface water via rainfall. Tropospheric half-lives of twenty weeks (Pearson and McConnell, 1975) to 8 years (McConnell and Schiff, 1978) indicate that MC is highly stable in the troposphere. Dilling et. al., (1976) estimated the decomposition rate of MC under simulated atmospheric conditions to be less than 5% in 23.5 hours. It is generally accepted that the larger the tropospheric residence time of a chemical species, the greater is the likelihood of its diffusion into the stratosphere (U.S. EPA, 1980b). In a recent study of the impact of chloro and chlorofluoro compounds on stratospheric ozone, based on atmospheric measurement data, the NAS concluded (1979) that MC contributes one quarter to one half as many chlorine atoms to the stratosphere as do CFC's 11 and 12; at the 1976 global emission rate MC is estimated (NAS, 1979) to destroy 8 to 15 percent as much ozone as do both CFC 11 and 12. Thus, release from improperly disposed solid wastes containing MC may pose a possible threat to the environment.

IV. PERSISTENCE

MC is inert to reaction with oxygen under normal conditions, except at high temperatures. There are two laboratory studies of the hydrolysis of MC (Dilling, 1975; Pearson and McConnel, 1975). These studies used two different methods for calculating the hydrolytic half life (U.S. EPA, 1980c). The hydrolytic half-life is about 5-9 months in freshwater, and about 39 months in sea water (Pearson and McConnel, 1975; U.S. EPA, 1980c).

At ambient temperatures MC hydrolyzes to acetic and hydrochloric acids. Vinylidene chloride (a CAG listed carcinogen) is a minor product, except at 10°C and at slightly alkaline pH when it is the major product of hydrolysis (Pearson and McConnell 1975, U.S. EPA, 1980c).

MC undergoes photochemical oxidation (Dilling et. al., 1975; Appleby, 1976; U.S. EPA, 1980c), yielding estimates for global average residence time of 1.4 to 12 years (U.S. EPA, 1980c). From these estimated lifetimes it was inferred that between 10 and 20 percent of the MC molecules produced will reach the stratosphere.

V. PHARMACOKINETICS

A. Absorption

The chloroethanes are rapidly absorbed following oral or inhalation routes of exposure (U.S. EPA, 1980a). Slow dermal absorption of 1,1,1-trichloroethane has been demonstrated in humans (Stewart and Dodd, 1964).

B. Distribution

Stahl, et al. (1969) have noted the presence of 1,1,1-trichloroethane in the liver, brain, kidney, muscle, lung and blood in post-mortem tissue samples following high levels of exposures. MC accumulates in the liver, kidney, and brain of the mouse following inhalation exposure (Holmberg, et. al., 1977).

C. Metabolism

The metabolism of chloroethanes involves both enzymatic dechlorination and hydroxylation to corresponding alcohols (U.S. EPA, 1979a). Oxidation reactions may produce unsaturated metabolites which are then transformed to the alcchol and ester (Yllner, 1971a,b,c,d). Trichloroethanol and trichloroacetic acid have been identified in the urine of rats following inhalation exposure to 1,1,1-trichloroethane (Ikeda and Ohtsuji, 1972). Metabolism appears to involve the mixed-function oxidase system (Van Dyke and Wineman, 1971).

D. Excretion

The chloroethanes are excreted primarily in the urine and expired air (U.S. EPA, 1980). Monster and coworkers (1979) reported that 60-80 percent of 1,1,1-trichloroethane inhaled by volunteers was expired unchanged; two urinary metabolites represented 3 percent of the uptake. Excretion of the chloroethanes is generally rapid, the majority of compound being eliminated within 24 hours (U.S. EPA, 1980a).

VI. EFFECTS

A. Carcinogenicity

The NCI (1977) conducted a bioassay of MC using mice and rats. Although a variety of neoplasms were observed, no relationship was established bewteen dosage groups, species, sex type of neoplasm or site of occurence. The shortened life spans of the test animals due to the toxicity of the chemical made an assessment of carcinogenicity impossible (NCI, 1977). The NCI and a manufacturer of MC are currently retesting the compound for carcinogenicity.

Price et. al., (1978), have demonstrated *in vitro* transformation of rat embryo cells by MC. Injection of these cells *in vivo* produced undifferentiated fibrosarcomas at the site of inoculation in all tested animals.

B. Mutagenicity

Several groups have investigated the mutagenicity of MC in the Ames assay. Henschler et. al. (1977) found MC inactive both with and without addition of microsomes, using TA-100 strain of *S. typhimurium.* Simmon et. al. (1977) used slightly different assay conditions and reported that MC is slightly mutagenic to this strain. A dose response was evident, and metabolic activation did not alter mutagenicity.

C. Teratogenicity

Schwetz et. al. reported (1974, 1979) on inhalation studies (at 87.5 ppm) on pregnant mice and rats. A number of

skeletal abnormalities were noted, but these were of marginal statistical significance. Additional studies are needed.

MC, when injected into the air space of fertilized chicken eggs at 2, 3 and 6 days of incubation is embryotoxic (LD_{50} of 50-100 mM/egg), and induces a variety of birth malformations (Elovaora et. al.: 1979). Both these studies suggest that MC has teratogenic potential, and that further experiments should be performed to confirm this potential toxicity.

D. Other Reproductive Effects

Pertinent information could not be located in the available literature on other reproductive effects of 1,1,1-trichloroethane.

E. Chronic Toxicity (U.S. EPA, 1980b)

Inhalation exposure of healthy adults to the current TLV for MC (350 ppm) generally does not result in significant untoward physiologic effects. Studies of human exposure to 100-500 ppm have shown only subjective symptoms of light-headedness, syncope, mild headache and nausea, and objective symptoms of eye, nose and throat irritation. No significant clinical chemistry organ function tests (e.g. liver function) have been noted. However, adverse effects on the performance of manual tasks have been documented.

At higher exposures (>10,000 ppm) MC produces anesthesia and cardiovascular effects which can be lethal. Animal studies, as well as accidental human exposure, have shown that

MC, at these high concentrations, produces a "chlorinated hydrocarbon" type of microscopic pathology of liver and kidneys (fatty infiltration and cellular necrosis) which is much less severe than that produced by carbon tetrachloride.

VI. AQUATIC TOXICITY

A. Acute Toxicity

For freshwater fish, 96-hour static LC_{50} values of 69,700 ug/l for the bluegill Lepomis macrochirus and 150,000 ug/l for the fathead minnow, Pimephales promelas, while a single 96-hour flow-through LC_{50} value of 52,800 ug/l was obtained for the fathead minnow, Pimephales promelas, (Alexander, et. al. 1978). For marine organisms, 96-hour static LC_{50} values ranged from 31,200 ug/l for the mysid shrimp, Mysidopsis bahia, to 70,900 ug/l for the sheepshead minnow, Cyprinodon variegatus, (U.S. EPA, 1978).

B. Chronic Toxicity and Plant Effects

Pertinent information could not be located in the available literature.

C. Residues

A bioconcentration factor of 9 was obtained for the bluegill (U.S. EPA, 1980a).

VIII. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor aquatic criteria derived by U.S. EPA (1980a), which are summarized below, have gone

through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

Based on mammalian toxicology data, the EPA (1979a) has prepared a draft ambient water quality criterion to protect human health at the level of 15.7 mg/l for 1,1,1-trichloroethane.

The 8-hour, TWA exposure standard established by OSHA for 1,1,1-trichloroethane is 350 ppm.

B. Aquatic

The freshwater criterion has been drafted as 5,300 ug/l as a 24-hour average, not to exceed 12,000 ug/l; while the criterion to protect marine life has been drafted as a 24-hour average concentration of 240 ug/l, not to exceed 540 ug/l.

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No. 165

1,1,2,-Trichloroethane

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

~~1981~~

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DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated 1,1,2-trichloroethane and has found sufficient evidence to indicate that this compound is carcinogenic.

1,1,2-TRICHLOROETHANE

Summary

Results of a National Cancer Institute carcinogenesis bioassay indicate that oral administration of 1,1,2-trichloroethane produces an increase of several tumor types in rats and mice.

Information is not available to indicate if 1,1,2-trichloroethane has any mutagenic effects, teratogenic effects, or adverse reproductive effects.

Animal studies have indicated that exposure to 1,1,2-trichloroethane may produce liver and kidney toxicity.

Aquatic toxicity data for 1,1,2-trichloroethane is limited, with only two acute studies in freshwater fish and invertebrates available. Toxic doses ranged from 18,000 to 40,200 µg/l.

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1,1,2-TRICHLOROETHANE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Chlorinated Ethanes (U.S. EPA, 1979a).

The chloroethanes are hydrocarbons in which one or more of the hydrogen atoms of ethane are replaced by chlorine atoms. Water solubility and vapor pressure decrease with increasing chlorination, while both density and melting points increase. 1,1,2-Trichloroethane (molecular weight 133.4) is a liquid at room temperature with a boiling point of 113°C, a melting point of -37.4°C, a specific gravity of 1.4405, and slightly soluble in water (U.S. EPA, 1979a).

The chloroethanes are used as solvents, cleaning and degreasing agents, and in the chemical synthesis of a number of compounds.

The chlorinated ethanes form azeotropes with water (Kirk and Othmer, 1963) and all are very soluble in organic solvents (Lange, 1956). Microbial degradation of the chlorinated ethanes has not been demonstrated (U.S. EPA, 1979a).

The reader is referred to the Chlorinated Ethanes Hazard Profile for a more general discussion of chlorinated ethanes (U.S. EPA, 1979b).

II. EXPOSURE

The chloroethanes are present in raw and finished waters primarily from industrial discharges. Small amounts of chloroethanes may be formed by chlorination of drinking water or treatment of sewage. A metropolitan water monitoring study has shown finished water levels from 0.1 to 8.5 µg/l for 1,1,2-trichloroethane (U.S. EPA, 1979a). Air levels of chloroethanes are produced by evaporation of volatile chloroethanes widely used as degreasing agents and in dry-cleaning operations (U.S. EPA, 1979a).

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Sources of human exposure to chloroethanes include water, air, contaminated foods and fish, and dermal absorption. Fish and shellfish have shown levels of chloroethanes in the nanogram range (Dickson and Riley, 1976).

Pertinent information was not found in the available literature on 1,1,2-trichloroethane levels in food.

The U.S. EPA (1979b) has estimated the weighted bioconcentration factor for 1,1,2-trichloroethane to be 6.3. This estimate was based on the octanol/water partition coefficient for 1,1,2-trichloroethane.

III. PHARMACOKINETICS

A. Absorption

The chloroethanes are absorbed rapidly following oral or inhalation routes of exposure (U.S. EPA, 1979a). Dermal absorption of 1,1,2-trichloroethane may be extensive as indicated by lethal toxicity in animals following dermal exposure (Smyth, et al. 1969).

B. Distribution

Specific information on the distribution of 1,1,2-trichloroethane has not been found in the available literature. The reader is referred to a more general treatment of the chloroethanes (U.S. EPA, 1979b) which indicates widespread distribution of these compounds throughout the body.

C. Metabolism

The metabolism of chloroethanes involves both enzymatic dechlorination and hydroxylation to corresponding alcohols (U.S. EPA, 1979a). Oxidation reactions may produce unsaturated metabolites which are then transformed to the alcohol and ester (Yllner, 1971). Trichloroethanol and trichloroacetic acid have been identified in the urine of rats following inhalation exposure to 1,1,2-trichloroethanol (Ikeda and Ohtsuji, 1972). Metabolism appears to involve the activity of the mixed function oxidase system (Van Dyke and Wineman, 1971).

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D. Excretion

The chloroethanes are excreted primarily in the urine and in expired air (U.S. EPA, 1979a) with excretion being generally rapid. Experiments conducted by Ullner (1971) indicate that following intraperatoneal injection of 1,1,2-trichloroethane into mice, more than 90 percent of the administered dose is excreted in 24 hours, with more than half found in the urine. Ten to twenty percent of injected compound is found in expired air.

IV. EFFECTS

A. Carcinogenicity

Results of an NCI carcinogenesis bioassay for 1,1,2-trichloroethane show that oral administration of compound produced an increase of several tumor types (NCI, 1978). Rats showed adrenal carcinomas, kidney carcinomas, and varied hemangiosarcomas, while mice showed an increase in hepatocellular carcinomas.

B. Mutagenicity, Teratogenicity and Other Reproductive Effects

Available information on this compound is very limited in these areas. A search of the literature did not reveal any pertinent data.

C. Chronic Toxicity

Animal studies have indicated that exposure to 1,1,2-trichloroethane may produce liver and kidney toxicity (U.S. EPA, 1979a).

V. AQUATIC TOXICITY

A. Acute Toxicity

The only aquatic toxicity data for 1,1,2-trichloroethane are single static bioassays on the bluegill (Lepomis macrochirus) and Daphnia magna. The acute 96-hour LC_{50} value for the bluegill was 40,200 µg/l, while the 48-hour LC_{50} value for Daphnia magna was 18,000 µg/l (U.S. EPA, 1979). Marine studies are presently not available.

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B. Chronic Toxicity, Plant Effects and Residues

Available information on this compound is very limited in these areas. A search of the literature did not reveal any pertinent data.

VI. EXISTING GUIDELINES AND STANDARDS

Neither the human health nor the aquatic criteria derived by U.S. EPA (1979), which are summarized below, have gone through the process of public review; therefore, there is a possibility that these criteria will be changed.

A. Human

Based on the NCI carcinogenesis data, and using a linear, non-threshold model, the U.S. EPA (1979a) has estimated the level of 1,1,2-trichloroethane in ambient water that will result in an additional cancer risk of 10^{-5} to be 2.7 µg/l.

The 8-hr, TWA exposure standard for 1,1,2-trichloroethane is 10 ppm.

B. Aquatic

The draft criterion for protection of freshwater aquatic life is 310 µg/l as a 24-hour average; the concentration should not exceed 710 µg/l at any time (U.S. EPA, 1979a). No criterion for protection of saltwater aquatic life has been found.

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~~1989~~

165-9

No. 166

Trichloroethylene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

~~1990~~

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SPECIAL NOTATION

U.S. EPA's Carcinogen Assessment Group (CAG) has evaluated trichloroethylene and has found sufficient evidence to indicate that this compound is carcinogenic.

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

TRICHLOROETHYLENE

SUMMARY

Trichloroethylene is a colorless liquid used mainly as a degreasing solvent. Both acute and chronic exposure to high levels of trichloroethylene produce central nervous system depression and other neurological effects. Trichloroethylene also causes some kidney and liver damage. Trichloroethylene has not been shown to be a teratogen, and the data suggesting mutagenicity and carcinogenicity are weak. The studies of mutagenicity and carcinogenicity have been complicated by the presence of contaminants with known carcinogenic and mutagenic activity. However, the cancer assessment group has determined that Trichloroethylene is carcinogenic.

Only a few studies have been reported on trichloroethylene toxicity to aquatic species. Fathead minnows, when exposed in flow through and static tests, had 96 hour LC_{50} values of 40,700 and 66,800 µg/l, respectively. The 96 hour LC_{50} for the bluegill was 44,700 µg/l in static tests. The 48 hour LC_{50} for the freshwater invertebrate, Daphnia magna, was 85,200 µg/l. In the only reported chronic test, no adverse effects were observed in Daphnia magna exposed to 10,000 µg/l. Photosynthesis was reduced by 50 percent in the alga, Phaedactylan tricornutum, at a concentration of 8,000 µg/l. Trichloroethylene was bioconcentrated 17-fold by the bluegill after 14 days exposure. The half life of this compound in tissues was less than 1 day.

TRICHLOROETHYLENE

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Trichloroethylene (U.S. EPA, 1979).

Trichloroethylene (C_2HCl_3, 1,1,2-trichlordethylene, TCE, molecular weight 131.4) is a clear, colorless liquid. Trichloroethylene has a water solubility of 1,000 µg/ml; a vapor pressure of 77 mm Hg and a melting point of 83°C (Patty, 1963). Trichloroethylene is mainly used as a degreasing solvent, and is used to lesser extents as a household and industrial dry-cleaning solvent, an extractive solvent in foods, and as an inhalable anesthetic during certain short-term surgical procedures (Huff, 1971).

Current Production: Annual production of trichloroethylene in the United States approximates 234,000 metric tons (U.S. EPA, 1979). The volatilization of trichloroethylene during production and use is the major source of environmental levels of this compound. Trichloroethylene is not expected to persist in the environment because of its rapid photooxidation in air, its low water solubility, and its volatility (Pearson and McConnell, 1975; Dillings, et al. 1976; Patty, 1963).

II. EXPOSURE

A. Water

The National Organics Monitoring Survey observed trichloroethylene in 28 of 113 drinking waters at a mean concentration of 21 µg/l in May through July, 1976 (U.S. EPA, 1979). Trichloroethylene may be formed during the chlorination of water (National Academy of Science, 1977; Bellar, et al. 1974).

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B. Food

There is little information concerning the occurence of trichloroethylene in U.S. foodstuffs. In England, trichloroethylene has been observed at concentrations up to 10 µg/kg in meats, up to 5 µg/kg in fruits, vegatables, and beverages (McConnell, et al., 1975); packets of tea were found to contain 60 µg/kg (Fishbein, 1976). Little trichloroethylene would be expected in other foodstuffs, except in the case where it is used as a solvent for food extractions. The U.S. EPA (1979) has estimated the weighted bioconcentration factor of trichloroethylene to be 39. This estimate is based on measured steady-state bioconcentration studies in bluegills and estimates of fish and shellfish consumption.

C. Inhalation

The only significant exposure to trichloroethylene in air occurs to a relatively small, industrially exposed population (Fishbein, 1976).

III. PHARMACOKINETICS

A. Absorption

Trichloroethylene is readily absorbed by all routes of exposure. In humans exposed to the compound by inhalation, steady state conditions are approached within two hours. Absorption of trichloroethylene following ingestion has not been studied in humans. In rats, at least 80 percent of an orally administered dose is systemically absorbed (U.S. EPA, 1979).

B. Distribution

In humans, trichloroethylene is distributed mainly to body fat (McConnell, et al. 1975). Laham (1970) demonstrated transplacental diffusion of trichloroethylene in humans.

C. Metabolism

Qualitatively the metabolism of trichloroethylene appears to be similar across species (Kimmerle and Eben, 1973). The principal products of trichloroethylene metabolism measured in urine are, trichloroethanol, trichloroacetic acid, and conjugated derivatives (glucuronides) of trichloroethanol. A reactive epoxide, trichloroethylene oxide, has been shown to be formed during the metabolism of trichloroethylene; it can alkylate nucleic acids and proteins (Van Duuren and Banerjee, 1976; Bolt and Filser, 1977). Patterns of metabolism of trichloroethylene in humans differ between male and female (Nomiyama and Nomiyama, 1971), and with age (U.S. EPA, 1979). Increased microsomal enzyme activity enhances the conversion of trichloroethylene to trichloroacetaldehyde (U.S. EPA, 1979). Ethanol interferes with the metabolism of trichloroethylene, causing ethanol intolerance in exposed workers (U.S. EPA, 1979).

D. Excretion

Trichloroethylene and its metabolites are excreted in exhaled air, urine, sweat, feces, and saliva (Kimmerla and Eben 1973; U.S. EPA, 1979). Trichloroethylene is lost from the body with a half-life of about 1.5 hours (Stewart, et al. 1962); however, its metabolites have longer half-lives ranging from 12 to 73 hours (Ikeda and Imamura, 1973; Ertle, et al. 1972).

IV. EFFECTS

A. Carcinogenicity

The National Cancer Institute (NCI, 1976) observed an increased incidence of hepatocellular carcinoma in mice (strain B6C3-F1) treated with trichloroethylene. Similar experiments in Osborne-Mendel rats failed to increase the incidence of tumors in this species. It has been pointed out that trichloroethylene used in the NCI bioassay (1976) contained traces of monofunctional alkylating agents, epichlorohydrin and epoxibutane, as stabilizers, and they might account for the observed carcinogenicity (U.S. EPA, 1979). No systematic study of humans exposed to trichloroethylene have revealed a correlation with cancer (Axelson, et al. 1978).

B. Mutagenicity

Trichloroethylene has been reported to be mutagenic, in the presence of mammalian liver enzymes, to a number of bacterial strains. These include E. coli K12, and S. typhimurium strain TA 100 (U.S. EPA, 1979: Simmon, et al. 1977), in addition to the yeast Saccharomyces cerevisiae (Shahin and VonBarstel, 1977). However, there is some doubt as to the mutagenicity of trichloroethylene due to epichlorohydrin and epoxibutane contamination. Henscher, et al. (1977) observed that these contaminants were potent mutagens in S. typhimurium strain TA100. Pure trichloroethylene was weakly mutagenic.

C. Teratogenicity

Exposure of mice and rats to 1600 mg/m^3 trichloroethylene for seven hours a day on days 6 through 15 of gestation did not produce teratogenic effects (Schwetz, et al. 1975).

D. Other Reproductive Effects

Pertinent data could not be located in the available literature.

E. Chronic Toxicity

Disturbances of the nervous system, which continue for at least a year after final exposure, were observed following industrial exposure to trichloroethylene (Nomiyama and Nomiyama, 1977; Bardodej and Vyskoch, 1956). Symptoms included headaches, insomnia, tremors, severe neuroasthemic syndromes coupled with anxiety states, and bradycardia. Prolonged occupational exposures to trichloroethylene have been also associated with impairment of the peripheral nervous system. This can include persistent neuritis (Bardodej and Vyskoch, 1956), temporary loss of tactile sense, and paralysis of the fingers (McBirney, 1954). Rare cases of hepatic damage have been observed following repeated abuse of trichloroethylene (Huff, 1971).

F. Other Relevant Information

Long-term toxicity of trichloroethylene appears to depend largely on its metabolic products (U.S. EPA, 1979). Chemicals that enhance or depress the mixed function oxidase system will have a synergistic or antagonistic effect, respectively, on the toxicity of trichloroethylene.

Trichloroethylene has been shown to induce transformation in a highly sensitive in vitro Fischer rat embryo cell system (F1706) (U.S. EPA, 1979). Following exposure of cells to 1 M trichloroethylene, the cells formed progressively growing foci made up of cells lacking contact inhibition, and the cells gained the ability to grow in semi-solid agar.

V. AQUATIC TOXICITY

A. Acute Toxicity

Alexander, et al. (1978) exposed fathead minnows (Pimephales promelas) to trichloroethylene in flow-through and static tests. The observed 96-hour LC_{50} values were 40,700 and 66,800 µg/l, respectively. The observed 96-hour LC_{50} for the bluegill (Lepomis macrochirus) is 44,700 µg/l in static tests (U.S. EPA, 1978). The 48 hour LC_{50} for Daphnia magna and is 85,200 µg/l (U.S. EPA, 1978). No saltwater fish or invertebrate acute toxicity data were found in the available literature.

B. Chronic Toxicity

In the only reported chronic test, no adverse effects were observed with Daphnia magna at the highest test concentration of 10,000 µg/l (U.S. EPA, 1978).

C. Plant Effects

There was a 50 percent decrease noted in ^{14}C uptake by the saltwater alga, Phaedactylum tricornutum, at a concentration of 8,000 µg/l (Pearson and McConnell, 1975).

D. Residues

Bioconcentration by bluegills was studied (U.S. EPA, 1978) using radiolabeled trichloroethylene. After 14 days the bioconcentration factor was 17. The half-life of this compound in tissues was less than one day.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The Food and Drug Administration (1974) has limited the concentration of trichloroethylene in final food products to 10 mg/kg in instant

coffee, 25 mg/kg in ground coffee and 30 mg/kg in spice extracts. The American Conference of Governmental Industrial Hygienists (ACGIH) TLV is 535 mg/m^3.

The Cancer Assessment Group (CAG) has determined that, at the present time, under existing policy, TCE is a carcinogen. The NCI bioassay (the results from which CAG has made their determination) is being repeated. When the data is available, it should be reviewed.

B. Aquatic

For trichloroethylene, the draft criterion to protect freshwater aquatic life is 1,500 µg/l as a 24-hour average; the concentration should not exceed 3,400 µg/l at any time. Criterion for saltwater species has not been developed because sufficient data could not be located in the available literature.

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TRICHLOROETHYLENE

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No. 167

Trichlorofluoromethane, Dichlorodifluoromethane and Trichlorotrifluoroethane Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

October 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documetns. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

TRICHLOROFLUOROMETHANE, DICHLORODIFLUOROMETHANE AND TRICHLOROTRIFLUOROETHANE

SUMMARY

Trichlorofluoromethane (F-11), dichlorofluoromethane (F-12) and 1,1,2-trichloro-1,2,2-trifluoroethane (F-113) are not easily degraded in the environment. After release at the surface of the earth, F-11 and F-12 and F-113 mix with the atmosphere and rise slowly into the stratosphere where they are decomposed by ultraviolet radiation to release chlorine atoms. The chlorine atoms react with ozone, thereby reducing the total amount of ozone in the stratosphere and permitting an increased amount of biologically active ultraviolet radation to reach the earth's surface. The accumulation of F-11, F-12 and F-113 in the atmosphere also increases the absorption and emission of infrared radiation (the "greenhouse" efect).

F-11, F-12 and F-113 are absorbed via the lungs, gastrointestinal tract, and skin, however, most of that which is absorbed is eliminated unchanged in expired air.

F-11 was not found carcinogenic in a long-term mouse study. The carcinogenic potential of F-113 has not been tested by NCI, and few specific studies have been documented. F-11, F-12 and F-113 were negative in the Ames *Salmonella* test; F-12 was positive in a *Neurospora crassa* test system.

At high concentrations in air, these compounds have been shown to induce cardiovascular and pulmonary effects in animals.

In March 1979, fully halogenated chlorofluoroalkanes (including F-11, F-12 and F-113) were banned as propellants in the United States except for essential uses. The action was taken because the chlorofluoroalkanes may deplete the stratospheric ozone, leading to various adverse effects.

I. INTRODUCTION

This paper is based on an EPA report entitled "Environmental Hazard Assessment Report: Major One- and Two-Carbon Saturated Fluorocarbons" (U.S. EPA, 1976a).

Trichlorofluoromethane and dichlorofluoromethane are commonly referred to by their fluorocarbon numbers, which are F-11 and F-12, respectively. This convention will be followed in this paper. 1,1,2-Trichlo-1,2,2-trifluoroethane is dubbed F-113.

F-11, a colorless volatile liquid, F-12, a colorless gas, and F-113, a non-flammable colorless liquid, have the following physical/chemical properties (U.S. EPA, 1976a, Downning, 1966).

	F-11	F-12	F-113
Molecular Formula	CCl_3F	CCl_2F_2	$CCl_2F\text{-}CClF_2$
Molecular Weight	137	120	187
Boiling Point (°C)	23.8	-29.8	47.6
Freezing Point (°C)	-111	-158	--
Solubility (gm/100gm H_2O, 0°C, 1 atm.)	soluble in water and many organic solvents		0.017

A review of the production range (includes importation) statistics for trichlorofluoromethane (CAS No. 75-69-4) which is listed in the initial TSCA Inventory (1979) has shown that between 100 million and 200 million pounds of this chemical were produced/imported in 1977.*

A review of the production range (includes importation) statistics for dichlorodifluoromethane (CAS No. 75-71-8) which is listed inthe initial TSCA Inventory (1979) has shown that between 200 million and 300 million pounds of this chemical were produced/imported in 1977*

The major uses of F-11 and F-12 are as aerosol propellants, refrigerants, and foaming agents (U.S. EPA, 1976a).

II. EXPOSURE

A. Environmental Fate

Although F-11 and F-12 volatilize quickly from water and soils, they are considered persistent in the environment due to their resistance to biodegradation, photodecomposition, and chemical degradation (U.S. EPA, 1975a). AFter release at the surface of the earth, F-11, F-12 and F-113 (as well as other chlorofluoromethanes) mix with the atmosphere and rise

*This production range information does not include any production/importation data claimed as confidential by the person(s) reporting for the TSCA Inventory, nor does it include any information which would compromise Confidential Business Information. The data submitted for the TSCA Inventory, including production range information, are subject to the limitations contained in the Inventory Reporting Regulations (40 CFR 710).

slowly into the stratosphere where they are decomposed by ultraviolet radiation to release chlorine atoms. Chlorine atoms and a subsequent reaction product, chlorine oxide, react with ozone and oxygen atoms, thereby reducing the total amount of ozone in the stratosphere and somewhat shifting the distribution of ozone toward lower altitudes. As a consequence, there is an increase in the amount of biologically active ultraviolet radiation (below 295 nm) reaching the earth's surface. In addition, the temperature distribution in the stratosphere is somewhat altered.

The accumulation of chlorofluoroalkanes in the atmosphere, at all levels, also increases the absorption and emission of infrared radiation (the "greenhouse" effect). This retards heat loss from the earth and thus affects the earth's temperature and climate. The amount of change in infrared absorption and emission is well known, however, the amount and details of the further effects on the earth's climate are uncertain. This effect is inevitably combined with the effects due to increased carbon dioxide in the atmosphere and works in the same direction (NAS, 1976, 1979).

B. Bioconcentration

While chlorofluoroethanes are quite lipophilic and have the potential to bioaccumulate in organisms, their high volatility appears to preclude significant bioaccumulation (U.S. EPA, 1975a).

C. Environmental Occurrence

Trichlorofluoromethane has been detected in finished drinking water, effluents from raw sewage and sewage treatment plants, and in rivers and lakes (U.S. EPA, 1976b). F-11 is formed in small quantities during chlorination and fluoridation of drinking water (U.S. EPA, 1975b).

The major routes by which the fluorocarbons reach the environment involve their commercial applications. Because of their characteristic high vapor pressures and low boiling points, it is expected that all losses of fluorocarbons would ultimately the atmosphere (U.S. EPA, 1976a).

III. PHARMACOKINETICS

The available data on fluorocarbon absorption and elimination indicate that they are absorbed across the alveolar membrane, gastrointestinal tract, and skin. Inhaled fluorocarbons are taken up readily by the blood. Fluorocarbons absorbed by any route are eliminated through expired air (U.S. EPA, 1976a).

Data from Allen and Hansbury, Ltd. (1971) show that subsequent to a five-minute exposure in ambient air, F-11 and F-12 are concentrated to the greatest extent in the adrenals, fat, and the heart of rats.

Eddy and Griffith (1971) observed metabolism in rats following oral administrations of ^{14}C-labelled F-12. About 2% of the total dose was exhaled as CO_2 and about 0.5% was excreted in urine; the balance was exhaled unchanged. Within thirty hours after administration, the fluorocarbon and its

metabolites were no longer present in the body. Blake and Mergner (1974) have indicated that the apparent resistance of F-11 and F-12 to biotransformation may be more a function of their rapid elimination rather than their general stability.

IV. HEALTH EFFECTS

A. Carcinogenicity

A bioassay of F-11 for possible carcinogenicity was conducted using rats and mice. Animals were subjected to F-11 by gavage for 78 weeks. The results of the bioassay in rats were not conclusive because an inadequate number of animals survived to the end of the study. Under the conditions of the bioassay, F-11 was not carcinogenic in mice (NCI, 1978). The carcinogenic potential of F-113 has not been dected by NCI, and few specific studies have been documented. Epstein et. al. (1967) observed a synergistic effect when piperonyl butoxide and F-113 were sumultaneously injected in mice, producing an increase in hepatoms.

B. Mutagenicity

Mutagenicity data on the fluorocarbons are scant. Neither of the compounds was mutagenic in Salmonella tester strains TA1535 or TA1538 with activation (Uehleke et al., 1977). Sherman (1974) found no increase in mutation rates over controls in a rat feeding study of F-12. Stephens et al., (1970) reported a significant mutagenic activity of F-12 in a Neurospora crassa test system. F-113 has not been shown to be positive in the Ames test, and was reported not to be mutagenic in the dominant

lethal test in the mouse.

C. Other Toxicity

Taylor (1974) noted that exposure to 7% oxygen-15% trichlorofluoromethane (F-11) caused cardiac arrhythmias in all rabbits exposed. F-11 was subsequently shown to exert its toxicity at air concentrations of 0.5-5% in the monkey and dog, and from 1-10% in the rat and mouse. In all these animals it induced cardiac arrhythmias, sensitized the heart to epinephrine-induced arrhythmias, and caused tachycardia (increased heart rate), myocardial depression, and hypertension. The concentrations of F-12 that sensitized the dog to epinephrine and that influenced circulation in the monkey and dog were similar to those reported for F-11, however, F-12 differed in its effects on the respiratory parameters. It caused early respiratory depression and broncho-constriction which predominated over its cardiovascular effects (Aviado, 1975a,b).

A possible increased sensitivity to the fluorocarbons in humans with cardiac or respiratory illness may exist, but this is difficult to determine definitively on the basis of animal studies. Azar et al. (1972) noted that human inhalation of 1,000 ppm (4,949 mg/m^3) F-12 did not reveal any adverse effect, while exposure to 10,000 ppm resulted in a 7% reduction in a standardized psychomotor test score.

V. AQUATIC EFFECTS

No data were found.

VI. EXISTING GUIDELINES

As of March 17, 1979, fully halogenated chlorofluoroalkanes were banned as propellants in the United States except for essential uses. The action was taken because the chlorofluoroalkanes (including F-11, F-12 and F-113) may deplete the stratospheric ozone, leading to an increase in skin cancer , climatic changes, and other adverse effects (43 CFR 11301).

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LB:42-2

No. 168

2,4,6-Trichlorophenol

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OCTOBER 30, 1980

DISCLAIMER

This report represents a survey of the potential health and environmental hazards from exposure to the subject chemical. The information contained in the report is drawn chiefly from secondary sources and available reference documents. Because of the limitations of such sources, this short profile may not reflect all available information including all the adverse health and environmental impacts presented by the subject chemical. This document has undergone scrutiny to ensure its technical accuracy.

2,4,6-TRICHLOROPHENOL

Summary

In a 1979 study N.C.I.-concluded that 2,4,6-trichlorophenol is carcinogenic in rats and mice. EPA's carcinogen Assessment Group has determined that there is substantial evidence that 2,4,6-trichlorophenol is carcinogenic in man.

2,4,6-Trichlorophenol is a convulsant and an uncoupler of oxidative phosphorylation.

2,4,6-Trichlorophenol is acutely toxic to freshwater fish with LC_{50} values ranging from 320 to 9,040 ug/l. No chronic or marine studies were available. Tainting of rainbow trout flesh has been noted at concentrations in water greater than 52 ug/l.

2,4,6-TRICHLOROPHENOL

I. INTRODUCTION

This profile is based on the Ambient Water Quality Criteria Document for Chlorinated Phenols (U.S. EPA, 1980).

2,4,6-Trichlorophenol (2,4,6-TCP) is a colorless, crystalline solid with the empirical formula $C_6H_3Cl_3O$ and a molecular weight of 197.5 (Weast, 1978). It has the following physical and chemical properties (Weast, 1978):

Melting Point:	69.5°C
Boiling Point:	246°C
Vapor Pressure:	1 mm Hg at 76°C
Solubility:	slightly soluble in water; soluble in alcohol and ether

Trichlorophenols are used as antiseptics and disinfectants, as well as for intermediates in the synthesis of other chemical products (U.S. EPA 1980).

It is generally accepted that chlorinated phenols will undergo photolysis in aqueous solutions as a result of ultraviolet irradiation and that photodegradation leads to the substitution of hydroxyl groups in place of the chlorine atoms and subsequent polymerization (U.S. EPA, 1980). For additional information regarding the chlorinated phenols, the reader is referred to the Hazrd Profile on Chlorinated Phenols (U.S. EPA, 1980).

II. EXPOSURE

Unspecified isomers of trichlorophenols have been detected in surface waters in Holland at concentrations of 0.003 to 0.1 ug/l (Piet and DeGrunt, 1975). 2,4,6-Trichlorophenol can be formed from the chlorination of phenol in water (Burttschell, et al. 1959). Exposure to other chemicals such as 1,3,5-trichlorobenzene,

lindane, the alpha- and delta-isomers of 1,2,3,4,5,6-hexachlorocyclohexane, and hexachlorobenzene could result in exposure to 2,4,6-trichlorophenol via metabolic degradation of the parent compound.

The U.S. EPA (1980) has estimated the bioconcentration factor 2,4,6-trichlorophenol to be 110 for the edible portion of aquatic organisms. This estimate is based on the octanol/water partition coefficient for this chemical.

Trichlorophenols are found in flue gas condensates from municipal incinerators (Olie, et al. 1977).

A. Absorption, Distribution and Metabolism

Information regarding the absorption, distribution and metabolism of 2,4,6-trichlorophenol could not be located in the available literature.

B. Excretion

In rats, 82 percent of an administered dose (1 ppm in the diet for 3 days) of 2,4,6-trichlorophenol was eliminated in the urine and 22 percent in the feces. Radiolabelled trichlorophenol was not detected in liver, lung, or fat obtained five days after the last dose (Korte, et al. 1978).

IV. EFFECTS

A. Carcinogenicity

Early studies on the tumor-promoting or-initiating capacities of 2,4,6-trichlorophenol were negative or inconclusive (U.S. EPA, 1980). Based on the results of its recent study, however, the NCI concluded that this compound is carcinogenic in male F344 rats (inducing lymphomas and leukemias), and in both

sexes of $B_6C_3F_1$ mice, inducing hepatocellular carcinomas and adenomas. (National Cancer Institute, 1979).

B. Mutagenicity

Ames tests using Salmonella, with and without mammalian microsomal activation, were negative for 2,4,6-trichlorophenol (Rasanen, et al. 1977). 2,4,6-Trichlorophenol increased the rate of mutations, but not the rate of intragenic recombination in a strain of Saccharomyces cerevisiae (Fahrig, et al. 1978). In addition, two of the 340 offspring from female mice injected with 50 mg/kg of 2,4,6-trichlorophenol during gestation were reported to have changes in hair coat color (spots) of genetic significance. At 100 mg/kg, 1 out of 175 offspring exhibited this response (U.S. EPA, 1980).

C. Teratogenicity, Other Reproductive Effects and Chronic Toxicity

Information regarding teratogenicity, other reproductive effects and chronic toxicity of 2,4,6-trichlorophenol could not be located in the available literature.

D. Other Relevant Information

2,4,6-Trichlorophenol is a convulsant (Farquharson, et al. 1958) and an uncoupler of oxidative phosphorylation (Weinbach and Garbus, 1965; Mitsuda, et al. 1963).

2,4,6-Trichlorophenol affects glucose metabolizing enzymes at low concentrations (U.S. EPA, 1980). At relatively high concentrations it affects the microsomal oxidizing system in vitro, which may have implication with respect to the liver's detoxification or cancer inducing abilities (U.S. EPA, 1980).

V. AQUATIC TOXICITY (U.S. EPA, 1980)

A. Acute Toxicity

Three assays have been conducted with 2,4-trichlorophenol to determine its acute toxicity to freshwater fish. A 96-hour static LC_{50} value of 600 ug/l has been obtained for the fathead minnow (Pimephales promelas). In a flow-through assay, a 96-hour LC_{50} value 9,040 ug/l was obtained for juvenile fathead minnows. The bluegill (Lepomis macrochirus) has been shown to be the most sensitive species studied, with a 96-hour static LC_{50} of 320 ug/l. Only one acute study has been performed on a freshwater invertebrate species. The result of a 48-hour static assay produced an LC_{50} value of 6,040 ug/l for Daphnia magna. There were no acute studies for any species of marine life.

B. Chronic Toxicity

2,4,6-Trichlorophenol is moderabely toxic to the fathead minnow (720 ug/l) (U.S. EPA, 1980).

C. Plant Effects

Complete destruction of chlorophyll in the algae, Chlorella pyrenoidosa, has been reported at concentrations of 10 ug/l. A chlorosis LC_{50} value of 5,923 ug/l was obtained for the duckweed, Lemna minor. Studies of the effects of 2,4,6-trichlorophenol on marine plants have not been reported.

D. Residues

No actual bioconcentration factors have been determined, but, based upon the octanol/water partition coefficient of 4,898, a bioconcentration factor of 380 has been estimated for those aquatic organisms having an eight percent lipid content.

The weighted average bioconcentration factor for the edible portions of all organisms consumed by Americans is estimated to be 110.

E. Miscellaneous

The tainting of fish flesh by 2,4,6-trichlorophenol has been observed in the rainbow trout (Salmo gairdneri). The highest estimated concentration of 2,4,6-trichlorophenol that will not impair the flavor of trout exposed for 48 hours to the chemical is 52 ug/l.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

Based on carcinogenicity the U.S. EPA (1980) has recommended 12 ug/l as the ambient for the 2,4,6-trichlorophenol water quality, criterion, for the ingestion of both fish and water (10^{-6} excess risk).

No other existing guidelines or standards were found for human exposure to 2,4,6-trichlorophenol.

B. Aquatic

The criterion to protect freshwater organisms 970 ug/l, is the chronic exposure value. Data were insufficient to derive a criterion for marine organisms (U.S. EPA, 1980).

2,4,6-TRICHLOROPHENOL

REFERENCES

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No. 169

1,2,3-Trichloropropane

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

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169-2

1,2,3-TRICHLOROPROPANE

Summary

Pertinent data are not available on the possible carcinogenicity, mutagenicity, teratogenicity, or chronic toxicity of 1,2,3-trichloropropane. Acute toxicity studies with animals suggest harmful effects to the liver. 1,2,3-Trichloropropane is reported to be irritating to the eyes and mucous membranes of humans.

Pertinent data on the toxicity of trichloropropane to aquatic organisms are not available.

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1,2,3-TRICHLOROPROPANE

I. INTRODUCTION

1,2,3-Trichloropropane (CAS registry 96-18-4) is a colorless, clear liquid made from the chlorination of propylene. It has the following chemical and physical properties (Windholz, 1976; Hawley, 1971; Verschueren, 1977):

Formula:	$C_3H_5Cl_3$
Molecular Weight:	147.43
Melting Point:	-14.7°C
Boiling Point:	156.85°C
Density:	1.3889^{20}_{4}
Vapor Pressure:	2.0 torr @ 20°C
Solubility:	Sparingly soluble in water, soluble in alcohol and ether.

1,2,3-Trichloropropane is used as a paint and varnish remover, solvent, and degreasing agent (Hawley, 1971), in addition to its use as a cross-linking agent in the elastomer Thiokol ST (Johnson, 1971).

II. EXPOSURE

A. Water

1,2,3-Trichloropropane has been detected in drinking water (U.S. EPA, 1975) and also in 6 of 204 surface water samples taken in various locations throughout the United States (U.S. EPA, 1977). No information concerning concentration was available.

B. Food

Pertinent data were not found in the available literature.

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C. Inhalation

Pertinent data were not found in the available literature; however, fugitive emissions from manufacturing and production facilities probably would account for the major portion of 1,2,3-trichloropropane if found in air.

D. Dermal

Pertinent data were not found in the available literature.

III. PHARMACOKINETICS

Pertinent data were not found in the available literature.

IV. EFFECTS

A. Carcinogenicity, Mutagenicity, Teratogenicity, Reproductive Effects, Chronic Toxicity.

Pertinent data were not found in the available literature.

B. Acute Toxicity

Exposure to trichloropropane at high concentrations is irritating to the eyes and mucous membranes and causes narcosis.

McOmie and Barnes (1949) exposed 15 mice to 5000 ppm trichloropropane for 20 minutes. Seven of the mice survived exposure; however, four of these mice died from liver damage 7 to 10 days later. Seven of ten mice exposed to 2500 ppm trichloropropane for 10 minutes per day for 10 days died. McOmie and Barnes (1949) found that liquid trichloropropane applied to the skin of rabbits produced irritation and erythema, followed by sloughing and cracking. Repeated application of 2 ml of trichloropropane caused a painful reaction, including subdermal bleeding, and the death of one of seven rabbits treated.

Silverman, et al. (1946) reported eye and throat irritation and an objectional odor to human volunteers exposed to 100 ppm trichloropropane for

15 minutes. McOmie and Barnes (1949) found that ingestion of 3g of trichloropropane by humans caused drowsiness, headache, unsteady gait, and lumbar pain.

V. AQUATIC TOXICITY

Pertinent data were not found in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The American Conference of Governmental Industrial Hygienists recommends a threshold limit value of 50 ppm for occupational exposure to 1,2,3-trichloropropane (ACGIH, 1977).

B. Aquatic

No guidelines on standards to protect aquatic organisms from 1,2,3-trichloropropane toxicity have been established because of the lack of pertinent data.

1,2,3-TRICHLOROPROPANE

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No. 170

o,o,o-Triethyl Phosphorothioate

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

DISCLAIMER

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O,O,O-TRIETHYL PHOSPHOROTHIOATE

Summary

There is no information available on the possible carcinogenic, mutagenic, teratogenic, or adverse reproductive effects of O,O,O-triethyl phosphorothioate. Triethyl phosphate, a possible metabolite of the compound, has shown weak mutagenic activity in Salmonella, Pseudomonas, and Drosophila.

Like other organophosphates, O,O,O-triethyl phosphorothioate may be expected to produce cholinesterase inhibition in humans.

No pertinent data are available on the aquatic effects of the compound.

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O,O,O-TRIETHYL PHOSPHOROTHIOATE

I. INTRODUCTION

O,O,O-Triethyl phosphorothioate (CAS registry number 126-68-1), also known as triethyl thiophosphate, is a colorless liquid with a characteristic odor. It has the following physical and chemical properties (Hawley, 1971):

Formula:	$C_6H_{15}O_3PS$
Molecular Weight:	198
Boiling Point:	93.5°C-94°C (10 torr)
Density:	1.074

O,O,O-Triethyl phosphorothioate is used as a plasticizer, lubricant additive, antifoam agent, hydraulic fluid, and as a chemical intermediate (Hawley, 1971).

II. EXPOSURE

A. Water and Food

Pertinent data were not found in the available literature.

B. Inhalation

Pertinent data were not found in the available literature; however, fugitive emissions from production and use would probably constitute the major source of contamination (U.S. EPA, 1977).

D. Dermal

Pertinent data were not found in the available literature.

III. PHARMACOKINETICS

A. Absorption

Pertinent data were not found in the available literature. Acute toxicity studies with a number of organophosphate insecticides indicate that these compounds are absorbed following oral or dermal administration

(Gaines, 1960). March, et al. (1955) have reported rapid absorption of the structurally similar insecticide demeton from the gastrointestinal tract of mice following oral administration.

B. Distribution

Pertinent data were not found in the available literature.

C. Metabolism

Pertinent data were not found in the available literature. The thiono isomer of the insecticide demeton may be metabolized via oxidative desulfuration by the liver at the P=S bond in mammals (March, et al. 1955) to form the thiolo derivative. Thus, O,O,O-triethyl phosphorothioate may be converted to triethylphosphate *in vivo* (Matsumura, 1975).

D. Excretion

Pertinent data were not found in the available literature. March, et al. (1955) have reported that following oral administration of demeton, the large majority of compound was eliminated as urinary metabolites, with small quantities detected in the feces. Elimination was rapid following oral administration.

IV. EFFECTS

A. Carcinogenicity

Pertinent data were not found in the available literature.

B. Mutagenicity

Pertinent data were not found in the available literature. The insecticide oxydemeton methyl has been shown to produce mutations in *Drosophila*, *E. coli* and *Saccharomyces* (Fahrig, 1974). Triethyl phosphate, a possible metabolite of O,O,O-triethyl phosphorothioate, has produced weak mutagenic effects in *Salmonella* and *Pseudomonas* (Dyer and Hanna, 1973) and recessive lethals in *Drosophila* (Hanna and Dyer, 1975).

C. Teratogenicity

Pertinent data were not found in the available literature. A single intraperitoneal injection of demeton (7 to 10 mg/kg) between days seven and twelve of gestation has been reported to produce mild teratogenic effects in mice (Budreau and Singh, 1973).

D. Other Reproductive Effects

Pertinent data were not found in the available literature. Embryotoxic effects (decreased fetal weights, slightly increased fetal mortality) have been reported following intraperitoneal administration of demeton (7 to 10 mg/kg) to pregnant mice (Budreau and Singh, 1973).

E. Chronic Toxicity

Pertinent data were not found in the available literature. O,O,O-triethyl phosphorothioate, like other organophosphates, may be expected to produce symptoms of cholinesterase inhibition in humans (NAS, 1977).

V. AQUATIC TOXICITY

Pertinent data were not found in the available literature.

VI. EXISTING GUIDELINES AND STANDARDS

Pertinent data were not found in the available literature.

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O,O,O-TRIETHYL PHOSPHOROTHIOATE

References

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No. 171

Trinitrobenzene

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APRIL 30, 1980

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DISCLAIMER

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TRINITROBENZENE

Summary

Information on the carcinogenicity, mutagenicity, teratogenicity, or adverse reproductive effects of trinitrobenzene was not found in the available literature.

Trinitrobenzene has been reported to produce liver damage, central nervous system damage, and methemoglobin formation in animals.

Slight irritant effects have been reported for marine fish exposed to trinitrobenzene at concentrations of 100 ug/l.

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TRINITROBENZENE

I. INTRODUCTION

This profile is based on the Investigation of Selected Potential Environmental Contaminants: Nitroaromatics (U.S. EPA, 1976).

Trinitrobenzene (1,3,5-trinitrobenzene, molecular weight, 213.1) is a crystalline solid with the following physical properties: melting point, 122.5°C; specific gravity, 1.76. The compound is explosive upon rapid heating. Trinitrobenzene is insoluble in water, but soluble in alcohol or ether (Windholz, 1976).

Trinitrobenzene is used as an explosive, and as a vulcanizing agent for natural rubber (U.S. EPA, 1976).

Hydrolysis of trinitrobenzene under neutral pH conditions is not expected to be rapid; as pH increases, hydrolysis would be favored (Murto, 1966). Photolytic degradation of trinitrobenzene has not been demonstrated in aqueous solutions (Burlinson, et al. 1973).

A bioconcentration factor is not available for trinitrobenzene; however, the work of Neely, et al. (1974) on several nitroaromatics would suggest a low theoretical bioconcentration of the compound.

Biodegradation of trinitrobenzene by acclimated microorganisms has been reported by Chambers, et al. (1963).

II. EXPOSURE

Pertinent information on levels of exposure to trinitrobenzene from occupational contact or from non-occupational sources of exposure (air, water, food) was not found in the available literature.

III. PHARMACOKINETICS

Pertinent information on the absorption, distribution, metabolism, or excretion of trinitrobenzene was not found in the available literature. The

reader is referred to a discussion of the pharmacokinetics of dinitrobenzenes, which may show pharmacokinetic similarities (U.S. EPA, 1979).

Acute oral toxicity studies conducted with dogs indicate that trinitrobenzene is effectively absorbed by this route (Fogleman, et al. 1955).

IV. EFFECTS

Pertinent information on the carcinogenic, mutagenic, teratogenic, or adverse reproductive effects of trinitrobenzene was not found in the available literature.

A series of toxicity studies in rats, mice, and guinea pigs have indicated that orally administered trinitrobenzene causes liver damage and central nervous system damage (Korolev, et al. 1977). The acute toxicity study of Fogleman, et al. (1955) has shown that trinitrobenzene, like dinitrobenzenes, induces methemoglobin formation in vivo.

V. AQUATIC TOXICITY

The only study reporting the effects of trinitrobenzene to aquatic life has been presented by Hiatt, et al. (1957). Slight irritant effects i.e., excitability, violent swimming, opercular movement increases suggesting respiratory distress upon short term exposure to marine fish Kuhlia sandvicensis were observed at exposure levels of 100 ug/l, while moderate and violent reactions to the chemical were produced at exposures of 1,000 and 10,000 µg/l. No effects were noted on exposures to concentrations of 50 or 10 ug/l.

VI. EXISTING GUIDELINES

There is no available 8-hour, TWA exposure limit for trinitrobenzene. The compound has been declared a hazardous chemical by the Department of Transportation (Federal Register, January 24, 1974).

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TRINITROBENZENE

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GPO 888-088

SJ40-6

No. 172

Aniline

Health and Environmental Effects

U.S. ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

October 30, 1980

DISCLAIMER

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ANILINE SUMMARY

Aniline is an aromatic amine. Like many members of this group it is characterized by an outstanding property: the ability to form methemoglobin in mammalian organisms. Aniline and some of its analogues have been suspected as carcinogens since the turn of the century. An increased incidence of urinary bladder tumors has been noted in workers in the aniline and aniline dyestuff industries. Oral feeding studies conducted by the National Cancer Institute have shown aniline to be carcinogenic in rats. Aniline is reported not to be mutagenic to six strains of S. typhimurium, however, several aniline analogues and derivatives are mutagenic.

ANILINE

I. INTRODUCTION

Aniline (aminobenzene) is a liquid at room temperature. Its physical properties can be summarized as follows: (Hawley, 1977; Weast, 1977-78; Strecher, 1968):

Molecular formula	$C_6H_5NH_2$
Molecular weight	93.13
Melting point	-6.2°C
Boiling point	184.4°C
Flash point	158.0°F (Closed Cup)
Solubility in cold water	35.0 grams/liter (0.38 M).
Temperature at which vapor pressure equals 1 mm/Hg	34.8°C
pKa	4.63

Of particular interest is aniline's water solubility - i.e., aniline is soluble even in cold water.

The Stanford Research Institute's Chemical Economics Handbook cites the nitrobenzene reduction process as the current method of aniline synthesis (McCaleb, 1976). It is estimated that 270,000 kkg of aniline was produced in 1978 (Slimak, et. al., 1980). Aniline was reported to be used for the following uses:

synthesis of isocyanate (50% of total consumption), of rubber chemicals (27%), dyes and intermediates (6%), hydroquinone (5%), drugs (37%), and miscellaneous chemicals including herbicides (9%).

II. EXPOSURE

A. Water

Aniline levels in surface or drinking water was not reported in the available literature. However, overall emission of aniline to receiving waters as a result of the production of aniline, consumptive use, carry-over as impurities in manufactured products, and degradation of manufactured products was estimated in 1978, to be 9970 kkg (Slimak, et. al., 1980).

B. Food

Pertinent data on aniline concentrations could not be located in the available literature.

C. Inhalation

Pertinent data on aniline concentrations could not be located in the available literature. However, overall emissions of aniline to air as a result of aniline, isocyanates, rubber chemicals, dyes and intermediates, hydroquinone, and miscellaneous products production is estimated to be 69.4 kkg in 1978 (Slimak, et. al., 1980). Aniline is also reported to occur in cigarette smoke (Gosselin, et. al., 1976).

PHARMACOKINETICS

A. Absorption

Both inhalation and dermal absorption are important exposure routes in humans (Pietrowski, 1957). At air concentrations of up to 20 mg/m^3, absorption is about equal by both routes, that is, 6 mg/hr; at higher concentrations the respiratory pathway becomes progressively a more important factor. Dermal contact with liquid aniline also results in rapid systemic absorption: 0.2-0.7 mg/cm^2 of skins/hr has been shown to occur (Pietrowski, 1957).

B. Distribution

Aniline is rapidly absorbed into the blood stream; its subsequent systemic distribution has not been reported. Its metabolic transformations (see below) are mainly dependent on liver enzymes.

C. Metabolism

Aniline is metabolized in the liver by oxidation and conjugation. Hepatic microsomal oxidizing enzymes cause metabolic transformation to N-acetylaminophenol and to o- and p-aminophenol. Conjugating enzymes then cause metabolic transformation to the glucuronide and sulfonate (Casarett and Doull, 1975).

D. Excretion

The administration of aniline leads to urinary excretion of glucuronic acid and sulfonic acid conjugates and of its metabolites, o- and p-aminophenol (Williams, 1959; Parke,

1960). In addition, small amounts of free aniline, phenyl sulfamic acid, aniline- glucuronide, aminophenyl and acetylaminophenyl, mercaptonic acids, phenylhydroxylamine, and acetanilide are excreted in varying amounts by different species tested (Parke, 1960). The conjugates of p-aminophenol are the most important urinary metabolites of aniline (Williams, 1959). The urinary excretion of these metabolites gives an accurate measure of the absorption of aniline vapor (Pietrowski, 1972). It is probable that the other aniline metabolites mentioned above also appear in the urine of people exposed to aniline (IARC, 1974).

IV. EFFECTS

A. Carcinogenicity

The carcinogenic potential of aniline has been of great interest because, since 1895, an increased incidence of urinary bladder tumors has been noted in workers in the aniline dye industry (IARC, 1974). It has subsequently been shown that other amines which occur in the environment, such as 2-naphthylamine, 4-aminobiphenyl and benzidine, are probably more important in the causation of these occupational cancers (IARC, 1974). Although most animal studies appear to have exonerated aniline as a human carcinogen (IARC, 1974), an NCI study showed a dose-related increase in fibrosarcomas or sarcomas in the spleen and in several organs of the body cavity. Although the results were not statistically significant, the rarity of these tumors and their dose-dependency

led to the conclusion that aniline is carcinogenic in female Fisher 334 rats. The male rats showed a statistically significant increase in the incidence of hemangiosarcomas of the spleen and a significant increase in the combined incidence of fibrosarcomas and sarcomas of the spleen and in multiple body organs (NCI, 1978).

B. Mutagenicity

In the Ames assay aniline is not mutagenic toward any of the six standard S. typhimurium strains, when tested in the presence or absence of microsomes (Geomet, 1980). However, in the presence of nor-harman (a 2-carboline derivative), significant mutagenicity has been observed (Nagao, et. al., 1977; Sugimura, 1979).

C. Teratogenicity

Pertinent data could not be located in the available literature. However, cyanotic effects such as those produced by aniline can adversely affect the fetus, leading the ITC to recommend that reproductive effect tests be conducted (44 FR 31871).

D. Other Reproductive Effects

Aniline can cross the placenta to form methemoglobin in the fetus, affecting its development (Gosselin, 1976). Courtney, (1979), reported that, after treatment of CD-1 mouse dams with aniline (150 to 200 mg/kg) during gestation and lactation, CPK and LDH isozyme patterns in serum and

cardiac tissue in offspring were altered on days 1 and 20 postpartum. The serum CPK pattern was markedly altered on day 1 postpartum and by day 20, an additional enzyme appeared.

E. Acute and Chronic Effects

Aniline is moderately lethal to the rat: the oral LD50 is 440 mg/kg. The LD50 value via the dermal route is 1400 mg/kg in the rat. For human beings the oral LDL0 is reported as 50 mg/kg (NIOSH, 1979). The no-effect level for humans has been estimated as 0.25 mg/kg (NIOSH, ref. 169).

Aniline absorption causes anoxia due to the formation of methemoglobin. Most of the signs and symptoms of overexposure to aniline can be attributed to methemoglobin formation. Such symptoms include fatigue, headache, irritability and dizziness (Proctor and Hughes, 1979). In addition there may be direct effects of aniline on the central nervous system (e.g., insomnia, paresthesias) and cardiotoxic effects (Patty, 1979; Sax, 1979).

Chronic exposure induces amenia (Patty, 1979; Sax, 1979; Proctor and Hughes, 1979). Other chronic effects of aniline exposure are hepatic injury, (perhaps caused by an aniline metabolite) (Jenkins, 1972; Geomet, 1980) and splenic hemosiderosis (NCI, 1978).

V. AQUATIC TOXICITY

The lethal concentration and threshold concentration for aniline with respect to Chironomus dorsalis Meig. larvae are 6 and 3 mg/l, respectively (Puzikova and Markin, 1975).

Aniline also produces toxic effects in Daphnia, at 0.4 mg/l (Verschueren, 1977).

B. Chronic Toxicity

Lakhnova 1975, reported that aniline at a concentration of 0.2 mg/l is lethal to Daphnia magna Straus within nine days. Therefore, Lakhnova recommended a maximum permissible limit of 0.02 mg/l.

VI. EXISTING GUIDELINES AND STANDARDS

A. Human

The maximum allowable concentration in class I waters for the production of drinking water in the U.S. is 5 mg/l. Several European countries have set lower limits: 0.1 mg/l (USSR), 5 ppm (Federal German Republic), 2.6 ppm (Deutsche Demokratische Republik), and 1.3 ppm (CSSR) (Verschueren, 1977).

B. Aquatic

Data were insufficient to draft a criterion for protection of freshwater or marine life. Lakhnova (1975) recommended a maximum permissible limit of 0.02 mg/l.

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